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American Heart Journal

VOL. 34 SEPTEMBER, 1947 NO. 3

Original Communications

PHYSIOLOGIC CHANGES IN THE CIRCULATION DURING AND AFTER OBSTETRIC LABOR

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SAN FRANCISCO, CALIF.

THE physiologic changes in the circulation which accompany and follow immediately after obstetric labor have not been studied in detail, although in terms of fatality and congestive failure the early puerperium is apparently the most critical period for patients with serious heart disease.[1a,b,2,3] In attempting to explain post-partum circulatory failure, two questions arise: (a) how important is the load imposed on the heart by the work of labor, and (b) what are the effects on the circulation of emptying the uterus, whether by cesarean section or by active labor?

The first question has been answered by the results of oxygen consumption studies[4] which showed that the work of labor is variable but often severe. For example, work may be performed which is equivalent to climbing a seven-foot flight of stairs once every three minutes during a labor lasting twelve hours. Furthermore, the "oxygen debt" incurred during a long and hard second stage may not be repaid for over an hour after delivery. The changes in pulse and respiratory rate which occur during labor[5,6] reflect the same situation. Work of this severity might be expected to precipitate failure of a functionally inadequate heart.

On the other hand, there is statistical evidence to show that emptying the uterus may in itself impose a burden on the heart. In patients with serious heart disease, deaths from congestive failure occur with equal or greater frequency

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following cesarean section, where the work of labor is excluded, than following vaginal delivery.[1c,7,8]

The effects of delivery on the circulation were studied by means of serial observations of several functions on individual patients, a method previously employed in investigating circulatory changes in pregnancy prior to labor.[9-11] Observations were made of heart rate, arterial and venous blood pressure, vital capacity, circulation time, plasma volume, and venous hematocrit at frequent intervals during labor and the early puerperium. In view of evidence presented by Burwell and co-workers[12,13] to suggest that the pregnant uterus functions as an arteriovenous shunt of important proportions, acute changes were looked for which might indicate occlusion of such a shunt at delivery.[14-18] The changes which were observed in normal patients and in three patients with heart disease, only one of whom was threatened by decompensation, were not sufficiently consistent to demonstrate the relative importance of (a) occlusion of a vascular shunt, (b) exercise, or (c) other factors in precipitating cardiac failure after delivery.

CLINICAL MATERIAL AND GENERAL PROCEDURE

Complete studies were made on thirteen normal and three cardiac patients who had uncomplicated vaginal deliveries and on two normal patients delivered by cesarean section without trial of labor. As soon as possible after the onset of labor, observations were made of pulse rate, blood pressure, venous pressure, vital capacity, circulation time, plasma volume, and hematocrit. These were repeated at two hours, six to twelve hours, twelve to thirty-six hours, two to three days, and four to eleven days after delivery. Two normal patients and one with heart disease delivered by the vaginal route and three normal patients delivered by cesarean section were studied in the same way except that plasma volume, hematocrit, and circulation time were not determined. Observations of pulse rate, blood pressure, and venous pressure were made at the usual times on nine patients who were delivered uneventfully by the vaginal route, but from whom oxytocic drugs were withheld until their need was evident, after which the effects of administration of these drugs were noted.

The patients were recumbent during all observations, and were in the fasting state except during the first twelve to twenty-four hours, during which a fat-free diet was given to ensure clear plasma. Records of fluid intake and output and of weight were kept as completely as possible. Labor was not extremely severe or prolonged in any patient, and blood losses, which were either measured or carefully estimated, were slight or moderate.

Most of the patients received barbiturates early in labor and inhalations of nitrous oxide-oxygen mixtures during pains in the second stage of labor. Two patients had caudal injections of metycaine, one pudendal, and one paravertebral nerve block. Local anesthesia was used for one cesarean section, and nitrous oxide-oxygen with ether or cyclopropane for the others. Following vaginal delivery, all patients received 1 c.c. of pituitrin or pitocin and 0.02 mg. of ergotrate (ergonovine maleate) intramuscularly, followed by 0.02 mg. of ergotrate orally every four hours for five doses, unless these drugs were specifi-

cally withheld. Following cesarean section, the initial .02 mg. of ergotrate was given intravenously.

METHODS

1. *Venous Pressure.*—The method of Moritz and von Tabora[19] was used, the zero point being placed 5 cm. dorsal to the angle of Louis. Care was taken to obtain complete muscular relaxation and to avoid obstruction of the vein by postural distortion, muscular contraction, or the weight of the breast. The presence of suitable conditions was indicated by free motion of the column of fluid with respiratory excursions. The first few readings made after insertion of the needle usually indicated a gradual fall in pressure, suggesting that muscular contractions or spasm of the vein occurred initially as a response to pain. After a constant low level was reached, repeated readings were usually identical and this final low pressure was recorded.

2. *Vital Capacity.*—This was measured in the supine position with a water spirometer. The best result of three good efforts was recorded.

3. *Circulation Time.*—Arm-to-tongue time was determined by the method of Winternitz, Deutsch, and Brüll,[20] using 3 c.c. of 20 per cent decholin.

4. *Hematocrit.*—Venous blood was collected without stasis at the beginning and end of each determination of plasma volume, a 1.4 per cent solution of potassium oxalate was added, and the specimen centrifuged for thirty minutes at 3,000 revolutions per minute. The average of each pair of readings was used.

5. *Plasma and Blood Volume.*—Plasma volume was determined by the method of Gibson and Evans,[21] using the Evelyn photoelectric colorimeter.[22] Six c.c. of 2 per cent T-1824 were injected for the first determination and from 2 to 6 c.c. for subsequent determinations. Blood samples were collected nine, twelve, and fifteen minutes after injection of the dye. Gross evidence of hemolysis was rarely seen, and if so, the specimens were discarded.

Difficulty was encountered in calculating plasma volumes from the data because of large variations in the slopes of the T-1824 time-concentration curves. In thirteen of the total of 103 determinations, the optical density of the fifteen-minute sample was less than that of the nine-minute sample of serum by an amount equivalent to 20 per cent or more of the plasma volume. This may have been due to (a) delayed mixing of the dye, or (b) loss of dye and plasma from the blood stream during the time in which samples were collected.[23] The results of of these thirteen determinations were discarded as technically unsatisfactory although they were of some interest in view of the possibility that considerable volumes of stagnant blood may be present in the legs, pelvis, or other vascular reservoirs about the time of delivery.[12] Under such circumstances, mixing of the dye might be expected to be abnormal.

In the remaining determinations, the difference in optical density between the first and last samples represented less than 10 per cent of the calculated plasma volume, but because satisfactory disappearance slopes could be plotted in only half of them, the readings of the nine-, twelve-, and fifteen-minute samples were

averaged. The necessity for making repeated determinations of plasma volume at intervals of only a few hours may have led to errors in the use of the photoelectric colorimeter because of the presence of residual dye in the control samples of serum.[23] Technical errors in administering the dye are apt to give high values for plasma volume with this method, but because suitable precautions were taken to avoid losses of dye, it seems unlikely that the extremely high values obtained in some of these experiments could have been due to such errors.

The total volume of circulating blood was calculated indirectly from plasma volume on the basis of the venous hematocrit. The results were only approximate because (a) the accuracy of the determinations of plasma volume was probably no better than 10 to 20 per cent, and (b) the relation between venous hematocrit and total body hematocrit was an unknown and, perhaps, variable factor.

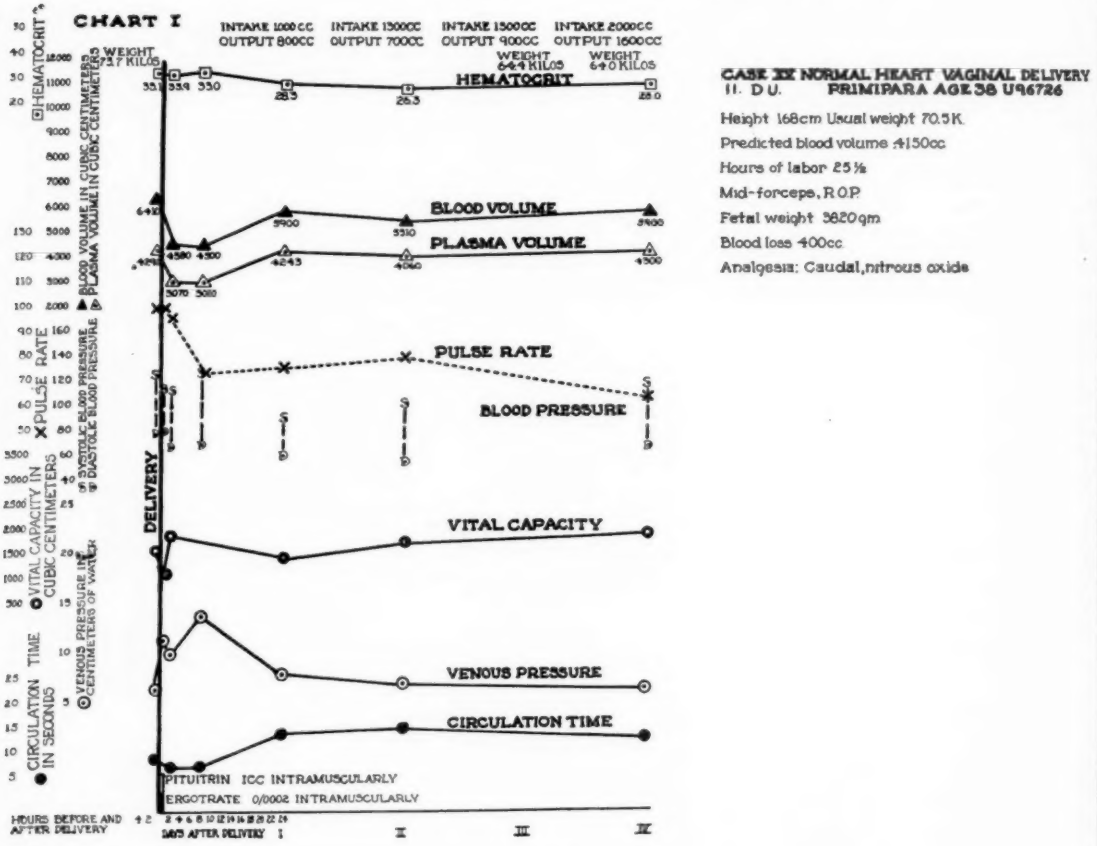

Chart I.

RESULTS

The results of each study were plotted as illustrated in Charts I to IV. A fairly typical series of observations on a normal patient delivered by the vaginal route is shown in Chart I. Observations on a patient delivered by

cesarean section (Chart II) were not strikingly different except that the venous pressure remained elevated for a shorter time after delivery than occurred in the case of vaginal delivery, and the pulse rate was increased postoperatively. Chart III illustrates the course of a patient with inactive rheumatic heart disease, free aortic regurgitation, and moderate cardiac enlargement, whose functional capacity was only slightly limited prior to pregnancy and who progressed uneventfully through pregnancy and delivery. Except for high pulse pressure and

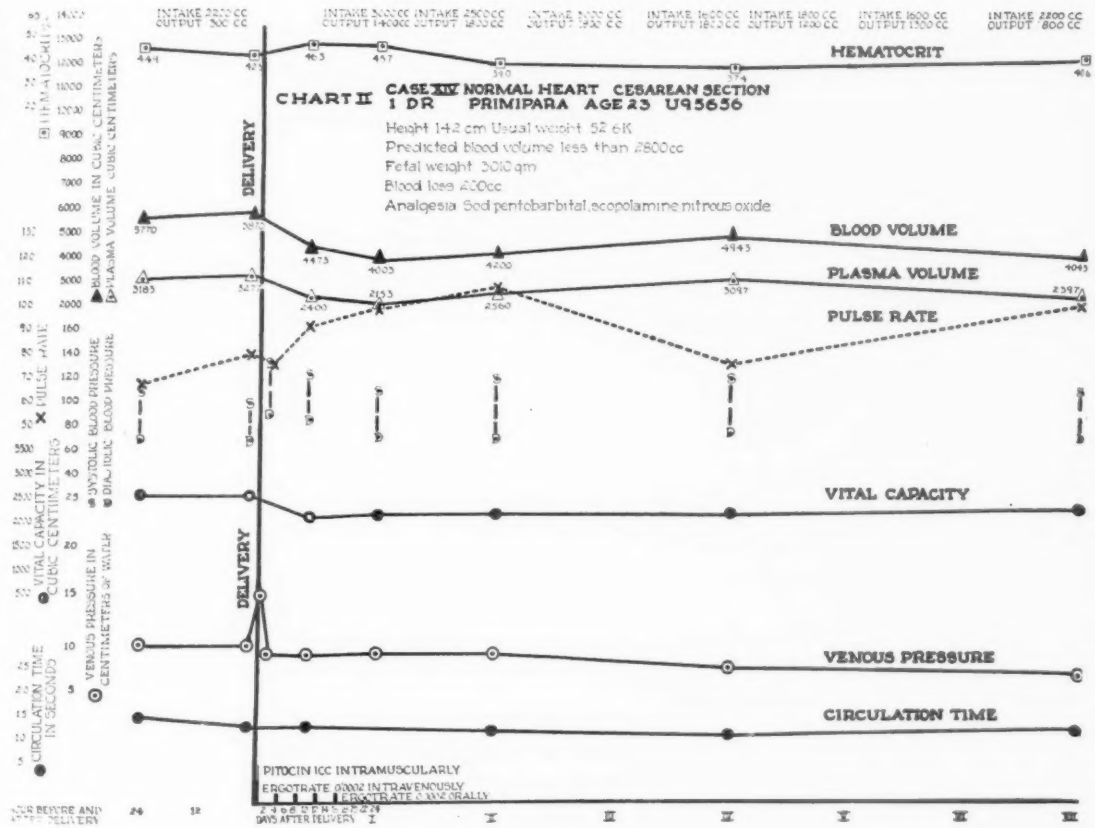

Chart II.

slightly accelerated pulse rate, this patient's course could not be differentiated from that of a normal individual by inspection of the chart. In Chart IV is shown the course of a patient with subacute bacterial endocarditis who was followed for several months before delivery. The large fluctuations of blood volume were attributed to marked wasting and anemia which developed between the March and April observations, and to the onset of left ventricular failure just prior to delivery. Basal lung râles were heard two hours after delivery and on the second post-partum day. The most striking features of the chart are the unusually prompt and extreme rise of venous pressure and the sharp drop in

pulse rate immediately post partum, even though the remainder of the patient's course was characterized by marked tachycardia.

For purposes of comparison, the changes taking place in individual functions were analyzed separately.

1. *Pulse Rate.*—Prompt slowing of the heart rate, which is the usual occurrence following occlusion of arteriovenous fistulas, did not appear regularly after deliveries involving active labor. A decrease of 10 beats or more per minute

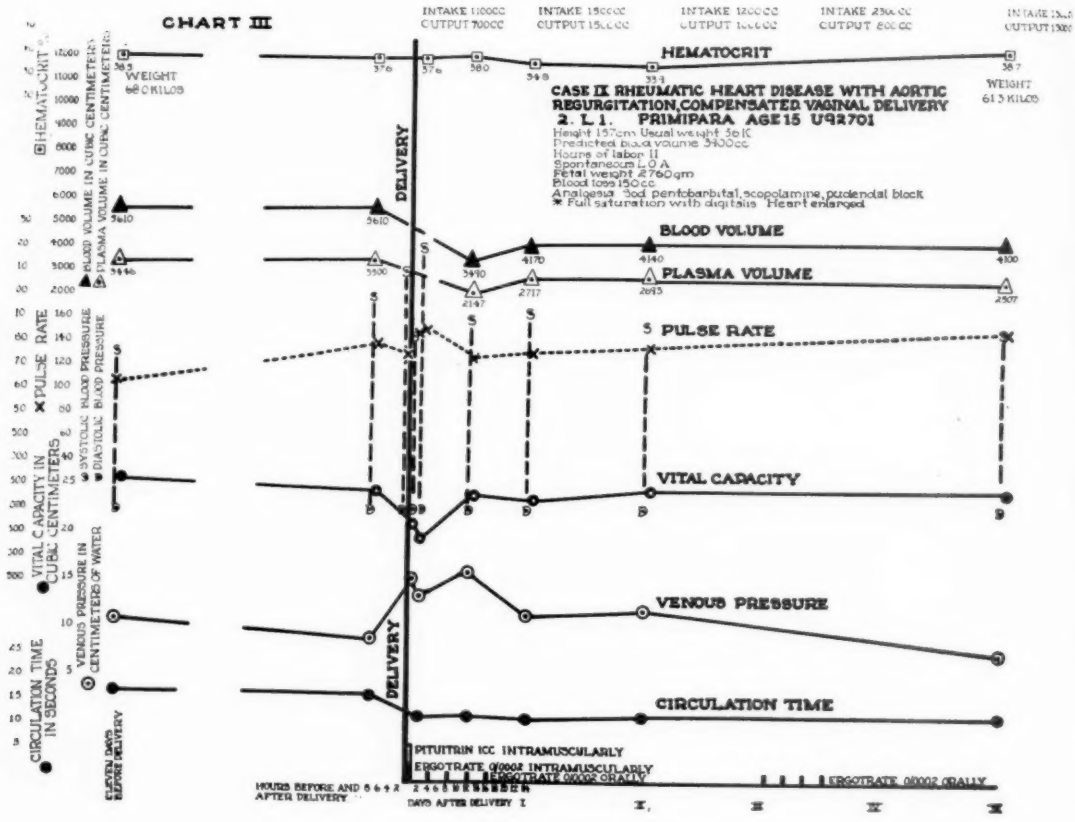

Chart III.

was observed at thirty minutes in only seven out of twenty-three and at two hours in only eleven out of twenty-four normal patients having vaginal deliveries. Significant decreases in pulse rate occurred even less frequently among the patients who received no oxytocic drugs than in those receiving the usual rations.[24] When delivery was not preceded by the work of labor, a post-partum decrease in pulse rate occurred more frequently. In three of the four cases delivered by cesarean section, the pulse rate had decreased more than 10 beats per minute by thirty minutes after removal of the fetus. It was possible to obtain counts just before and after removal of the fetus in only two of these cases. In one, the

rate decreased 20 beats (local anesthesia), and in one it increased 8 beats per minute (inhalation anesthesia).

2. *Blood Pressure.*—A post-partum increase in diastolic blood pressure would have been evidence to support the shunt hypothesis, but neither diastolic nor systolic pressure was affected regularly by delivery. At thirty minutes after delivery, there was an increase in diastolic pressure of 5 mm. Hg or more in only eight out of twenty-three, and at two hours, in only four out of twenty-four

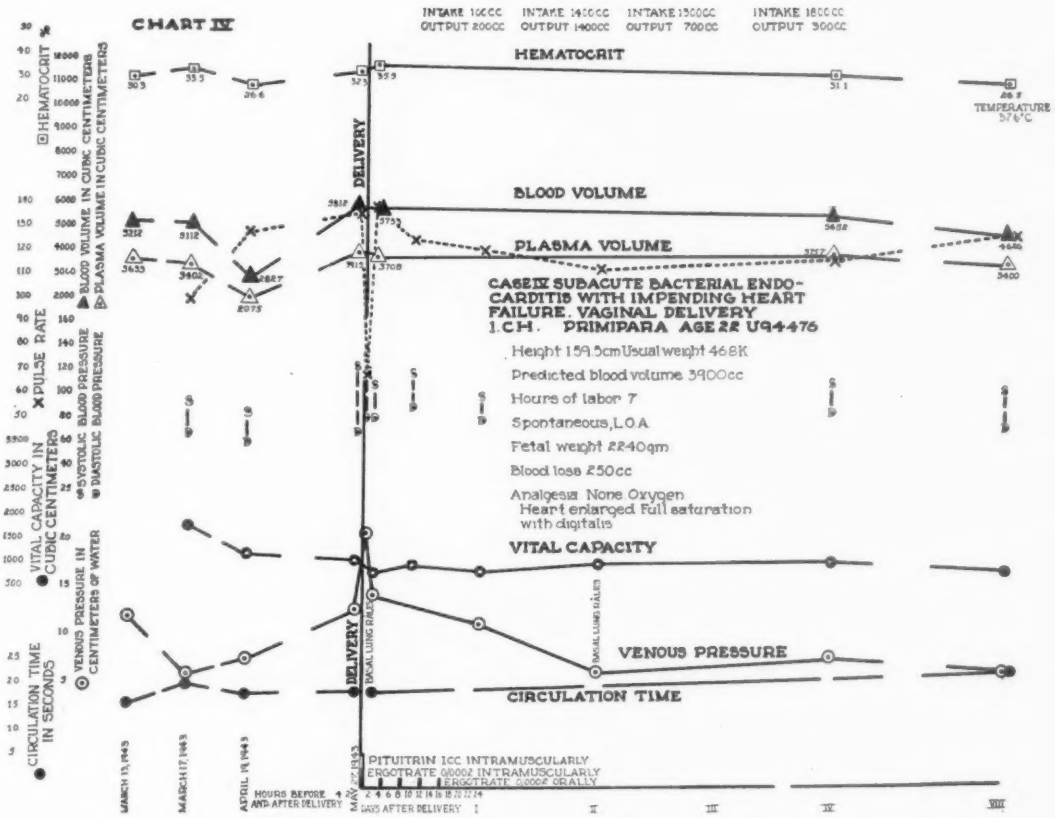

Chart IV.

normal patients delivered by the vaginal route. After cesarean section, diastolic pressure was increased by the same amount in one out of three patients at thirty minutes, and in three out of four at two hours.

3. *Venous Pressure.*—Among the normal patients who had vaginal deliveries, the venous pressures found during the first stage of labor were below the normal limit of 12 cm. H_2O, or slightly elevated (Table I). In the second stage, all the pressures which were measured between pains were within normal limits,

TABLE I. VENOUS PRESSURE IN CENTIMETERS OF WATER BEFORE AND AFTER DELIVERY

	BEFORE DELIVERY		AFTER DELIVERY					
	STAGE I	STAGE II	30 MINUTES	2 HOURS	6-12 HOURS	12-36 HOURS	2-3 DAYS	4-11 DAYS
Vaginal deliveries of normal patients with oxytocic drugs								
1 (Ol.)	6.5	5.5	14.0*	13.5*	13.5*	7.0	10.5	8.5
2 (Sc.)	9.3	8.5	10.0*	11.0*	12.0*	13.0	12.0	12.5
3 (To.)	8.7	——	15.0*	22.0*	8.5*	——	7.5	8.5
4 (Bu.)	10.5	——	9.0*	15.0*	11.5*	10.0*	8.5	6.5
5 (Fr.)	8.0	9.0	8.0*	17.0*	11.7*	11.5	11.0	17.5*
6 (Za.)	13.0	——	13.5*	19.0*	24.0*	22.0*	16.0	9.5
7 (St.)	12.5	——	15.5*	19.5*	18.3*	17.5	10.0	10.5
8 (Ny.)	7.8	7.4	15.5*	14.0*	12.0*	6.2	6.0	7.5
9 (Cl.)	12.5	——	——	17.0*	14.0*	14.5	13.0	12.5*
10 (Wa.)	8.0	8.0	13.0*	12.0*	10.7*	6.5	——	6.8
11 (Du.)	6.5	10.5	11.3*	10.0*	13.8*	8.0	7.0	6.5
12 (Ba., L.)	9.5	——	10.8*	12.3*	11.7*	14.0*	11.3	10.5
13 (Sa.)	9.0	——	13.5*	24.0*	19.0*	11.0	11.5	9.0
14 (Ba., J.)	10.5	——	7.5*	19.0*	25.5*	16.0*	11.0	10.0
15 (Vi.)	8.0	——	8.8*	10.5*	11.5*	8.3	7.2	9.5

*Ergotrate taken within four hours.

Vaginal deliveries of normal patients without oxytocic drugs								
1 (Os.)	11.5	——	8.0	8.5	9.5	8.7	9.0	9.0
2 (Jo.)	10.0	10.0	9.5	10.5	8.8	10.8	9.0	8.0
3 (Cow.)	5.0	——	5.8	6.0	6.0	7.3	7.3	7.0
4 (Si.)	5.5	——	7.8	8.8	8.0	7.3	8.3	6.8
5 (El.)	9.8	——	9.3	8.8	7.5	8.0	8.0	8.5
6 (Ma.)	14.0	——	8.5	9.3	9.0	8.0	——	——
7 (Dr.)	8.5	——	9.5	8.5	11.5	11.0	8.5	——
8 (Sl.)	12.0	——	13.0	11.5	13.0	12.8	10.5	——
9 (Wh.)	10.3	——	10.0	7.5	11.5	8.5	——	——
Vaginal deliveries of patients with heart disease with oxytocic drugs								
1 (Ch.)	12.5	——	20.5*	14.0*	——	11.0	6.0	5.8
2 (Li.)	9.0	——	15.2*	13.5*	16.0*	11.5	12.0	7.5
3 (Cog.)	11.2	10.0	11.2*	16.0*	12.5*	9.5	9.2	10.0
4 (Gr.)	9.0	14.0	14.0*	20.0*	17.0*	11.8	8.5	8.5
Cesarean sections of normal patients with oxytocic drugs	BEFORE OPERATION							
1 (Dr.)	9.8		15.0*	9.5*	8.9*	9.0	9.0	6.8
2 (Cop.)	9.5		20.5*	8.0*	14.0*	9.5*	7.8	——
3 (Cr.)	9.5		16.0*	12.5*	12.0*	10.5	10.5	9.3
4 (Re.)	7.5		18.0*	14.0*	13.0*	12.0*	11.0*	11.0
5 (Wa.)	10.5		15.5*	17.0*	7.5*	10.5	13.0	9.5

*Ergotrate taken within four hours.

although very high pressures were found on a few occasions when measurements were made during uterine contractions.[25]

In every normal patient who received oxytocic drugs, a rise of venous pressure occurred within two hours after delivery, the pressure reaching a level of 12 cm. water or above in twelve out of fifteen instances. In patients with abnormal hearts similar changes occurred, the elevation being higher and more prolonged in the one patient (*Ch.*) with cardiac failure. Fig. 1 illustrates the serial changes in venous pressure which occurred in individual patients. The

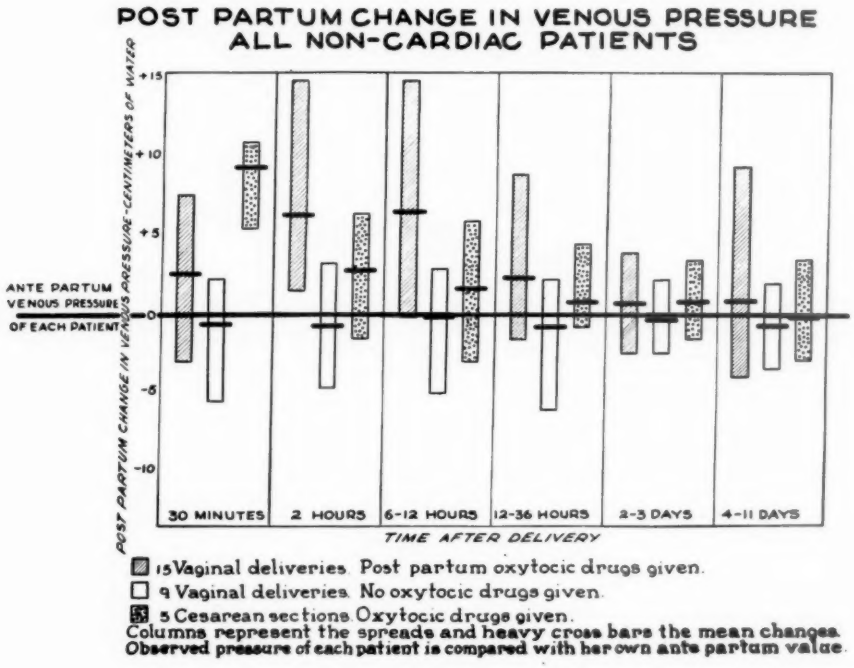

Fig. 1.

shaded columns representing normal vaginal deliveries show that at two hours after delivery, every patient had had a rise of venous pressure, the mean increase being 6.4 cm. water. The elevation was still present six to twelve hours after delivery but in most cases the venous pressure had returned to the ante-partum level by the second or third post-partum day.

To determine whether or not the work of labor was responsible for this rise of venous pressure, detailed studies were made of the changes in venous pressure following cesarean section. After delivery of the fetus there was a uniform increase in venous pressure, which was more immediate and more extreme but of shorter duration than that observed after vaginal deliveries (Table I, Fig. 1). Measurements of venous pressure were made during four abdominal deliveries by attaching the manometer through a three-way stopcock to a slow intravenous

drip of saline so that the infusion could be interrupted and pressures determined every few minutes. Patient *Cr.*, who received local anesthesia, showed a rise of pressure from 12.5 to 18.0 cm. within five minutes, and patient *Re.*, who had received general anesthesia, showed a rise from 14.8 to 18.0 cm. within three minutes after removal of the fetus. In the other two patients, the results were complicated by the effects of inhalation anesthesia.

The post-partum rise of venous pressure was therefore not caused by the work of labor. It seemed possible that the action of oxytocic drugs might be responsible because: (a) the elevations of pressure appeared earlier and were more marked when ergotrate had been given intravenously, and (b) the high pressures found after vaginal delivery were usually coincident with the recent administration of ergotrate. (Pressures measured within four hours of such medication are identified in Table I by means of asterisks.) It was found, moreover, that when the usual rations of ergotrate and pituitary preparations were not given at the time of delivery, there was no post-partum rise of venous pressure (Table I, Fig. 1).

The effects of administration of oxytocic drugs later in the puerperium were studied in the nine patients from whom they had been withheld at the time of delivery. The usual doses of pituitrin had no perceptible effect on venous pressure, pulse, or blood pressure on two occasions. The results of ergotrate administration are summarized in Table II. When this was given orally in repeated doses, a significant elevation of venous pressure was present as late as eight to twenty-two hours after the beginning of treatment, but when an intramuscular dose accompanied the first of a similar series of oral doses, the elevations of venous pressure which occurred early were not sustained. Finally, when ergotrate was given to nonpuerperal hospital patients, both women and men, increases in venous pressure of 2.0 cm. H_2O or more occurred within thirty minutes to two hours after injection in four out of seven instances (Table II). These results appeared to confirm the suspicion that the administration of ergotrate was responsible for the rise of venous pressure which was usually observed post partum, and suggested that this effect might be the combined result of (a) autotransfusion caused by contraction of the uterus,[26] and (b) decreased capacity of the vascular reservoir.

4. *Vital Capacity.*—The results obtained during labor and especially within twelve hours after delivery appeared to be related to the general state of the patient as evidenced by such factors as fatigue, preoccupation, and drowsiness, although cooperation was generally good. As compared with the values observed during labor, seven of thirteen normal patients delivered by the vaginal route showed decreases of between 100 and 900 c.c., while five showed increases of 150 to 500 c.c. at the two-hour observation. In one, no change was observed. By the time of the final observation at four to eleven days after delivery, nine out of twelve showed increases of 100 to 1,000 c.c. and three showed decreases amounting to between 100 and 250 cubic centimeters.

5. *Circulation Time.*—Before delivery, arm-to-tongue circulation time in the thirteen normal patients having vaginal deliveries varied between 9.0 and

TABLE II. CHANGES IN VENOUS PRESSURE FOLLOWING ORAL AND INTRAMUSCULAR ADMINISTRATION OF ERGONOVINE MALEATE

	DAYS AFTER DELIVERY	RESTING VENOUS PRESSURE (CM. H_2O)	ROUTE OF ADMINISTRATION*	NUMBER OF DOSES†	CHANGE IN VENOUS PRESSURE 30 MINUTES TO 2 HOURS AFTER INITIAL DOSE (CM. H_2O)	CHANGE IN VENOUS PRESSURE 8½ TO 22 HOURS AFTER INITIAL DOSE (CM. H_2O)
Puerperal patients						
1 (Os.)	8	9.0	Oral	3	−0.8	+2.8
2 (Jo.)	4	9.0	Oral	2	—	+3.0
3 (Co.)	6	7.5	Oral	3	+5.0	+5.5
4 (Si.)	4	6.8	Oral	5	—	+6.0
5 (El.)	3	8.0	Oral Intramuscular	5 1	+3.0	+1.0
6 (Ma.)	2	7.8	Oral Intramuscular	1 1	+4.0	—
7 (Sl.)	1 (20 hours)	12.8	Oral Intramuscular	4 1	+4.3	−2.3

8 (Wh.)	1 (12 hours)	11.5	Oral Intramuscular	4 1	+6.5		+0.3
					30 MINUTES	2 HOURS	
Nonpuerperal females							
1 (Sc.)		10.8	Intramuscular	2‡	+11.7 (nausea)	+9.7	+2.2
2 (Gi.)		9.0	Intramuscular	2‡	+0.5	−0.5	—
Males							
1 (Bl.)		8.0	Intramuscular	2‡	+1.0	—	—
2 (Ar.)		4.8	Oral Intramuscular	1 1	+2.0	+1.0	—
3 (Sa.)		10.3	Oral Intramuscular	1 1	+2.7	+4.2	—
4 (Sm.)		6.0	Intramuscular	2‡	+2.0	+4.0	0
5 (Sim.)		5.0	Intramuscular	2‡	+2.0	+4.0	+1.0

*When both routes were used, intramuscular injection was at the same time as first oral dose.
†Oral dose was 0.2 mg., repeated every 4 hours. Intramuscular dose was 0.2 mg., given once.
‡0.4 mg. given in 1 injection.

18.0 seconds, or an average of 12.6 seconds, which is close to the average normal of 13.0 seconds reported by Tarr, Oppenheimer, and Sager.[27] Two hours after delivery, the values varied between 7.0 and 20.0, with an average of 11.6 seconds. At the last observation, four to eleven days post partum, the average was 14.4 and the variation between 11.0 and 23.0 seconds. In certain individuals an unusually short circulation time during labor became even shorter two hours after delivery. This is reflected in the average values for the group. There was an

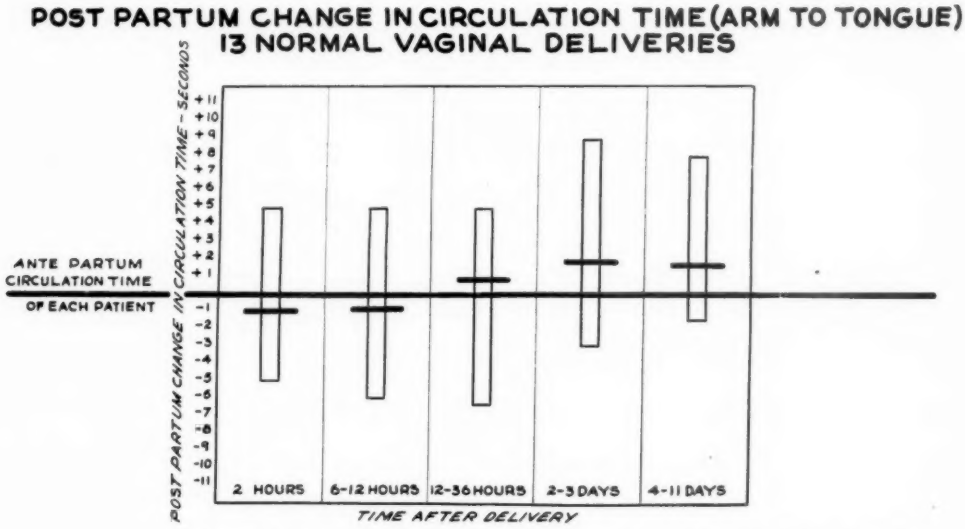

Fig. 2.

overall trend toward acceleration during the first twelve hours, followed by a gradual return to normal rates of circulation during the puerperium, but, as illustrated by Fig. 2, the actual changes which occurred were small and the direction of the changes far from uniform. Following cesarean section and in the patients with cardiac disease, the changes were substantially the same.

6. *Hematocrit.*—The results are shown in Table III. Post-partum hemoconcentration occurred in eight out of the thirteen normal patients who were delivered by the vaginal route and received oxytocic drugs, in two out of three patients with cardiac disease, and in each of two patients delivered by cesarean section. During the puerperium, the hematocrit percentage usually fell and then rose to approach the intra-partum reading. It is to be noted that approximately 180 c.c. of blood were taken from each patient in the course of five to seven determinations of plasma volume.

TABLE III. HEMATOCRIT PER CENT BEFORE AND AFTER DELIVERY

	BEFORE DELIVERY	AFTER DELIVERY				
	STAGE I	2 HOURS	6-12 HOURS	12-36 HOURS	2-3 DAYS	4-11 DAYS
Vaginal deliveries of normal patients						
1 (Ol.)	38.2	41.8	40.3	38.2	36.4	40.4
2 (Sc.)	38.7	40.7	41.2	40.4	41.7	39.3
3 (To.)	32.9	36.0	35.0	35.5	——	32.1
4 (Bu.)	37.5	41.8	39.2	39.3	37.9	38.5
5 (Fr.)	36.6	34.8	34.1	35.0	35.8	35.2
6 (Za.)	41.5	42.8	40.6	42.4	34.8	38.8
7 (St.)	33.0	34.8	34.4	34.6	32.0	32.6
8 (Ny.)	41.8	——	40.4	37.8	38.7	39.1
9 (Cl.)	40.0	39.3	37.3	38.4	33.6	39.0
10 (Wa.)	38.0	36.4	35.9	37.0	37.0	36.6
11 (Du.)	33.1	31.9	33.0	28.3	26.3	28.0
12 (Ba., L.)	44.0	47.2	46.5	46.1	46.6	50.4
13 (Sa.)	43.4	46.7	46.6	42.1	38.5	39.1
Vaginal deliveries of patients with heart disease						
1 (Ch.)	32.3	35.5	——	——	——	26.5
2 (Li.)	38.5	37.6	38.0	34.8	33.9	38.7
3 (Cog.)	36.0	40.6	37.9	34.0	35.6	37.9
	BEFORE OPERATION					
Cesarean sections of normal patients						
1 (Dr.)	44.9	42.3	46.3	45.7	39.0	40.6
2 (Cr.)	40.6	——	43.3	45.2	43.5	43.3

7. *Blood Volume.*—Approximate values for total blood volume, expressed to the nearest 100 c.c., are shown in Table IV. All results are included except those which were discarded because of steep time-concentration curves, hemolysis, or opacity of the serum. In six out of seven cases of normal vaginal delivery, the ante-partum blood volume exceeded the volume predicted for the patient on the basis of her height by 18 to 77 per cent of the predicted volume. If the extremely high two-hour value in Case 10 is disregarded, comparison can be made between the ante-partum value and that found two hours after delivery in four cases of normal vaginal delivery. The volume had decreased 10 per cent or more of the initial value in three cases and increased in one. Six to twelve hours after delivery, the situation was essentially the same. The general tendency toward reduction in blood volume during the first twelve hours after delivery is illustrated further by the two cases of heart disease and one of cesarean section (Table IV), all of whom showed decreases of more than 10 per

TABLE IV. TOTAL BLOOD VOLUME, CALCULATED FROM PLASMA VOLUME AND VENOUS HEMATOCRIT, BEFORE AND AFTER DELIVERY*

	BEFORE DELIVERY	AFTER DELIVERY						
						LAST DETERMINATION		PREDICTED VOLUME BASED ON HEIGHT† C.C.
	LABOR—STAGE I C.C.	2 HOURS C.C.	6-12 HOURS C.C.	12-36 HOURS C.C.	2-3 DAYS C.C.	VOLUME C.C.	DAYS AFTER DELIVERY	
Vaginal deliveries normal patients								
1 (Ol.)	5200	——	5900	5300	5900	8500	9	3920
2 (Sc.)	4600	4100	4800	5800	——	3800	4	3900
3 (To.)	——	4300	4100	4500	——	5400	4	3900
4 (Bu.)	——	——	4100	4700	4600	4000	7	3880
5 (Fr.)	6900	4200	5200	——	4900	4300	4	3920
6 (Za.)	——	9600	6800	5900	5300	4800	6	3820
7 (St.)	——	5100	5500	4700	5400	4700	6	4080
8 (Ny.)	5000	——	4600	4400	4000	4800	5	3900
9 (Cl.)	——	——	——	——	——	8300	4	3980
10 (Wa.)	5900	10000	6200	——	——	8100	6	3900
11 (Du.)	6400	4600	4500	5900	5500	5900	4	4150
12 (Ba., L.)	——	5900	7100	6200	6900	5200	6	3600
13 (Sa.)	3700	4200	3900	4200	4200	3800	6	3750
Vaginal deliveries patients with heart disease								
1 (Ch.)	——	5700	——	——	——	5500	8	3900
2 (Li.)	5600	——	3500	4200	4100	4100	5	3900
3 (Cog.)	8100	——	7300	——	7100	5000	5	4000
	BEFORE OPERATION							
Cesarean sections normal patients								
1 (Dr.)	5800	5900	4500	4000	4200	4000	7	2800
2 (Cr.)	——	——	9700	5600	4700	6600	5	3980

*Expressed to nearest 100 cubic centimeters.

†Data from Gibson, J. G., Jr., and Evans, W. A., Jr.: J. Clin. Investigation **16**:317, 1937.

cent. Considering all ten cases in which comparison at either two hours or six to twelve hours was possible, blood volume had decreased 10 to 38 per cent in five, increased 13 per cent in one, and was within 10 per cent of the ante-partum value in four cases at the six- to twelve-hour observation. Contrary to expectation, there was no general tendency for the volumes to fall toward normal by the time of the last examination; in fact, extremely high volumes were found four to nine days post partum in several instances. Transient secondary increases in volume occurred between the two-hour and the final observation in several cases.

DISCUSSION

In general, the results are consistent with, but do not prove, the hypothesis that an arteriovenous shunt of important proportions exists in the pelvis at term and that the consequences of its obliteration may contribute to the load imposed on the circulatory system by delivery. This concept is attractive because it provides an orderly pattern into which most of the observations can be arranged, as has been done in interpreting the circulatory changes manifested during pregnancy prior to labor.[12]

The absence of a consistent reduction in heart rate immediately after vaginal delivery does not exclude the possibility of a shunt because in this series of patients, as well as that reported by Pardee and Mendelson,[5] the heart rate was modified by other factors such as the work of labor, anesthesia, and the effects of oxytocic drugs. The greater tendency to reduction in pulse rate immediately after emptying the uterus by cesarean section, noted also by Burwell and associates,[13] indicates the possible importance of these factors. It is likely that changes in the blood pressure, such as might be expected to occur after removal of a shunt, are masked in the same way. The slight changes in blood pressure which take place during pregnancy[13,28,29] are consistent with the shunt hypothesis but may be attributed equally well to increased metabolic rate.

The determinations of vital capacity were included as a basis for future management of patients with heart disease and as an aid to interpreting other findings relative to cardiac failure. In normal patients, no relationship was found between the post-partum rise in venous pressure and changes in vital capacity. A decrease in vital capacity early in the puerperium, followed later by an increase such as occurred in these cases, has also been reported for two larger series.[30,31] The changes were attributed to mechanical factors affecting ventilation rather than to circulatory embarrassment.

Among several studies of venous pressure in pregnancy and the puerperium,[12,32-35] observations of the changes taking place in the first twenty-four hours after delivery have been reported only by Dellepiane[33] and Luisi.[34] The increased pressure in the antecubital vein observed during this period has been attributed to the effects of lactation.

On the basis of the shunt hypothesis, some elevation of systemic venous pressure after obliteration of the placental circulation might be anticipated without consideration of the action of oxytocic drugs. The situation would be

analogous to that reported by Holman,[15b] who found transitory cardiac enlargement immediately after occlusion of large arteriovenous fistulae in dogs. Even a normal heart might not be able to accommodate the augmented venous return incident to the severe exercise of labor[4,36] at a time when overall resistance was increased abruptly following occlusion of a shunt. Transitory cardiac dilatation and high venous pressure might exist until filtration of fluid at high capillary pressures had reduced the volume of circulating blood to fit the vascular compartment.

The experimental results indicate, however, that at least in women with normal hearts, no such transient decompensation follows evacuation of the uterus. The post-partum increase in venous pressure was not immediate and often did not appear until the time of the two-hour examination; and, furthermore, other signs of circulatory embarrassment, such as tachycardia, decreased vital capacity, and increased circulation time usually were not present during periods when venous pressure was maximal.

The results of the studies in which ergotrate was withheld post partum and in which the effects of its administration to puerperal and nonpuerperal patients were observed, indicate that the large and sustained elevations of venous pressure which were seen in all normal patients during the first twenty-four hours after deliveries at which the usual medications were given were caused, at least in part, by the actions of oxytocic drugs. To the reduction in capacity of the vascular tree generally attributed to these agents[24] may be added other factors which may have been present to contribute to the high venous pressure, that is, (a) increased return of blood to the heart from exercising muscles,[36] (b) autotransfusion of blood expressed from the uterus by the action of oxytocic agents,[26] and (c) a possible increase in overall resistance coincident with occlusion of a vascular shunt.

All of these volume factors might be expected to contribute to the precipitation of congestive failure in patients with limited cardiac functional capacity. It has been shown[37] that during the uterine contractions of normal labor, arterial inflow to the placenta is greatly diminished and blood contained in the placenta squeezed out. These repeated small autotransfusions might cause transient rises of venous pressure, thus producing filtration of fluid from the capillaries so that total blood volume was gradually diminished during labor. No such gradual preparation for obliteration of the placental circulation is possible in the case of abdominal delivery, which may account for the more prompt rise of venous pressure after abdominal than after pelvic delivery in normal patients (Fig. 1) and also explain, at least in part, the mortality associated with cesarean section in patients with cardiac disease.

In certain cases of congenital heart disease with potential right-to-left intracardiac shunt, alarming situations have been observed to arise at delivery, which were apparently due to increased shunting of the pulmonary circuit.[38] When the presence of such lesions is suspected, efforts should be made to avoid sudden increases in the volume of blood presented to the right side of the heart; the slow process of normal labor might be expected to be tolerated better than

abrupt delivery. Furthermore, it would appear that in cases of this type, as well as in others with limited cardiac reserve, the use of ergot derivatives should be reserved for hemorrhagic emergencies.

The changes observed in arm-to-tongue circulation time were not conclusive. However, it is noteworthy that a decided decrease in circulation time occurred on several occasions at times when venous pressure was elevated and maximal hemoconcentration was present. The acceleration which occurs in pregnancy prior to the onset of labor has been attributed by Cohen and Thomson[39] to hemodilution and by Burwell[12] to the presence of the placental shunt. The post-partum decrease in the circulation time might reflect a relative increase in the volume of blood passing through cutaneous anastomoses. This interpretation is consistent with the results of plethysmographic studies[40] in which it was found that blood flow through the muscles of the forearm was unchanged during pregnancy, but that in the hand, where numerous arteriovenous anastomoses exist, blood flow was greatly increased in some patients, not only during pregnancy, but for several weeks after delivery. The part played by metabolic factors in these phenomena has not been demonstrated.

Hemoconcentration had occurred in three-fourths of the cases between the initial determination and that made two hours after delivery. This change and the subsequent hemodilution which appeared with greater uniformity are in agreement with more complete studies, the most recent of which is that of Crawford.[41] On the basis of changes in packed cell volume, plasma protein concentration, and average cell size, and assuming an initial blood volume of 5,000 c.c., he calculated that an average of 590 c.c. of fluid was lost from the blood stream prior to the maximum intrapartum concentration and an average of 745 c.c. was gained to account for the secondary hemodilution. By the end of the second puerperal week, the blood picture had returned to normal.

Although it is well known that blood volume is increased during pregnancy and returns to normal late in the puerperium,[9,42,43] almost no measurements of blood volume have been made just before and after delivery to confirm this indirect evidence that there is a redistribution of fluid between intravascular and extravascular spaces at this time. Albers,[44] in an incomplete report, describes an early post-partum decrease in blood volume followed by an increase with hemodilution just prior to the diuresis. Crawford's data indicated that the initial depletion of plasma volume may occur either just before, during, or just after delivery, and this may account for the fact that a significant reduction in plasma volume was shown by comparing the ante partum with the first or second post-partum value in only half of the cases of the present series. The secondary increase in volume was more uniform and often striking. The final determinations of plasma and blood volume may have been made too early to show the return to normal which has been found by other investigators.[43]

The initial movement of fluid from vascular to extravascular spaces is more likely to be controlled by hemodynamic than humoral factors because it occurs so much earlier than the post-partum diuresis which is usually observed on the third to fifth day.[45,48] The exact time at which the depletion of plasma volume

occurs after occulsion of large arteriovenous fistulas[14,17,18] has not been demonstrated; but it is possible that in both this situation and obstetrical delivery the decrease in circulating blood volume results from a sudden increase in overall resistance following obliteration of a shunt. Other factors which may be in operation during labor are (a) osmotic movement of water to exercising muscles, (b) sweating, and (c) filtration through capillary walls during periods of venous congestion, especially late in labor when periods of recovery between uterine contractions are short, and during the first few hours after delivery. For instance, using the unit rate of filtration obtained by Landis and Gibbon[46] for the human forearm during thirty-minute periods of venous congestion, it may be calculated that a person weighing 50 kilograms might lose 600 c.c. of fluid in the course of forty-three minutes while venous pressure was increased 10 cm. above the resting level.

Secondary hemodilution and increased blood volume, found almost uniformly in this series and by others[41,44] early in the first week of the puerperium may be partly the result of reabsorption of fluid lost to the tissues during labor but conceivably could be related to the process of removal of extracellular water during the period of negative sodium balance and diuresis.[45,47,48] More complete and accurate data are required to determine whether the very high blood volumes found on several occasions near the end of the first week of the puerperium were related to mobilization of fluid or were technical artefacts.

The presence of pulmonary edema in a patient with severe cardiac failure after delivery might lead to consideration of therapeutic phlebotomy. Among the arguments for and against this procedure it is important to consider that, in view of the immediate post-partum hemoconcentration, venesection at this time will deprive the patient of a disproportionately large oxygen-carrying capacity. Later in the puerperium, blood loss can be tolerated better.

The rapid rates of disappearance of the dye T-1824 after its injection for determinations of plasma volume, which led to difficulties in interpretation of the results, most often at the ante-partum observation but occasionally after delivery, have not been explained. Among factors which might be considered is the possibility that large pools of blood into which dye diffuses slowly and irregularly may exist in the pelvis, legs, or other reservoirs both before and after delivery. Demonstration of the presence of such pools would be of importance in explaining post-partum circulatory failure in cardiac patients because autotransfusion of this blood after occlusion of the placental circulation or after administration of oxytocic drugs in the puerperium would affect the volume of venous blood supplied to the heart. More complete studies of the technique of measuring blood volume under these unique conditions are in progress.

SUMMARY AND CONCLUSIONS

1. Repeated determinations of several circulatory functions were made during labor and after delivery in normal patients and in patients with heart disease to determine whether the load imposed on the heart by delivery is pri-

marily the result of (a) the work of labor, (b) more or less sudden obliteration of a vascular shunt in the uterus, or (c) a combination of these and possibly other factors.

2. The changes in heart rate, arterial blood pressure, vital capacity, and circulation time were not sufficiently uniform to point to definite conclusions.

3. Venous pressure increased significantly and often to abnormal levels during the first twenty-four hours after delivery in all patients who received routine medications. Further evidence indicated that this rise of venous pressure could be attributed to the effects of ergotrate. For reasons which have been outlined, it is recommended that ergot derivatives and probably posterior pituitary preparations as well be used with caution in all serious cases of heart disease, especially in the presence of congenital intracardiac shunts.

4. Unusual technical difficulties were encountered in attempting to measure plasma volume with the dye T-1824, both before and after delivery. The results of hematocrit determinations and of those estimations of blood volume which appeared to be technically satisfactory were in agreement with other available evidence indicating that (a) at about the time of delivery a significant volume of fluid leaves the vascular compartment; (b) on the second or subsequent days of the puerperium a volume even greater than this returns to the blood stream; and (c) the final return to normal nonpregnant blood volume probably occurs after this as a result of the post-partum diuresis.

5. Even though the evidence as a whole is inconclusive, the close analogy which has been demonstrated between the changes in blood volume, hematocrit, and venous pressure taking place at delivery and changes known to follow obliteration of large arteriovenous fistulas suggest that the uterus at term contains a shunt of important proportions. The repeated uterine contractions of normal labor, by temporary occlusion of the placental circulation, may prepare the cardiovascular system for permanent occlusion of the shunt. This may explain the clinical impression that vaginal delivery is tolerated as well as or better than cesarean section by patients with serious heart disease.

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VOLUNTARY ACCELERATION OF HEART IN A SUBJECT SHOWING THE WOLFF-PARKINSON-WHITE SYNDROME

Clinical, Physiologic, and Pharmacologic Studies

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VOLUNTARY acceleration of the heart has been reported and studied in at least twenty cases.[1-11] Most of the subjects have been students in physiology, medical students, or physicians. It is not unlikely that the incidence of voluntary acceleration of the heart may be much more frequent than the few cases in the literature suggest. We are reporting the twenty-first case. The subject (D. E. E., age 23), while an undergraduate student in medicine, discovered his ability to voluntarily speed his heart rate. We present this case report because of the unique association of the Wolff-Parkinson-White syndrome. Our work includes physiologic and pharmacologic studies made in an effort to elucidate the mechanism of the control of his heart rate and the accompanying symptoms.

CASE REPORT

Clinical History.—Two years before the present observations were undertaken, D. E. E. tried voluntarily to dilate his pupils by using the principle of the fear response. He decided to recall an emotion of fear—a frightening nightmare experienced four years previously when he was lost in the Canadian wilds. He wrote out his experiences and re-enacted them in his imagination. This experience was practised daily for four weeks, with intense concentration on the climax of the story. He observed the dilation of his pupils in a mirror and noted the accompanying sensations, which included tachycardia. After repeated experiences he was able to dissociate the effort to dilate his pupils and to concentrate on the will to accelerate his heart and found that he was successful. After an interval of a year he found again that he was able to control his heart rate at will. Upon concentration and the sudden acceleration of the heart he felt as if subjected to an explosion, and had paresthesia of the hands and feet, tinnitus, and palpitation. On willing his heart to slow he felt relaxed and had a sensation of relief and of fatigue. He frequently felt dissociated from his environment. Euphoria and a sensation of numbness often followed. The only other pertinent fact in the history was the occurrence of attacks of paroxysmal tachycardia five or six times a year, lasting two or three hours. These attacks started and stopped suddenly and were unrelated to any effort at voluntary acceleration. One of us (H. F.) observed the subject in one of these attacks. The rate was 180 per minute and the rhythm was regular. The attack had lasted thirty minutes before observation and was readily stopped by right carodit sinus pressure. No electrocardiogram was taken at this time.

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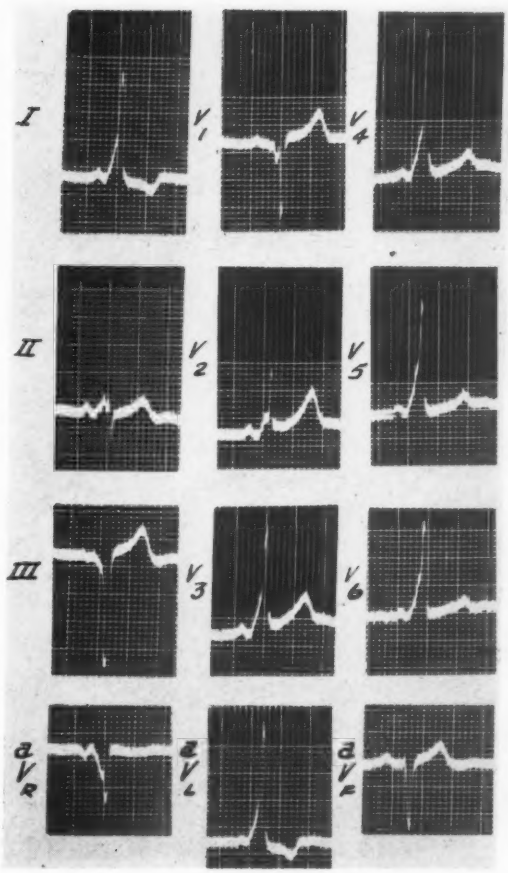

Fig. 1.—Electrocardiogram showing the characteristics of the Wolff-Parkinson-White syndrome.

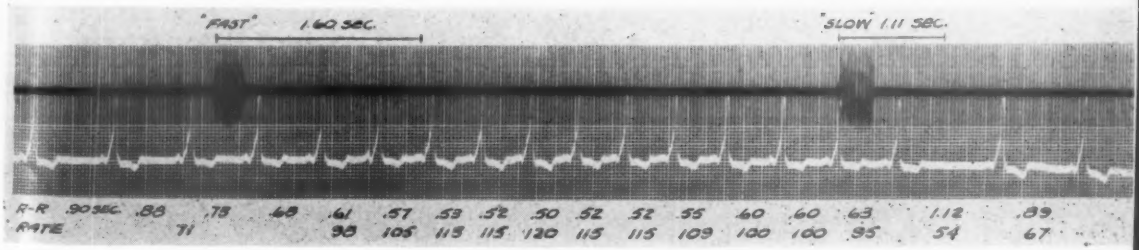

Fig. 2.—Electrocardiogram demonstrating voluntary speeding and slowing of the heart rate.

Examination.—Examination did not reveal any evidence of abnormality, except that the electrocardiogram was typical of the Wolff-Parkinson-White syndrome (short P-R interval and prolonged QRS complex). The chest leads placed this case in the "B" classification (Fig. 1) as described by Rosenbaum and associates.[12] The P-R interval is 0.10 second and the QRS interval is 0.13 second. The limb leads have the appearance of left bundle branch block. Lead V_1 shows that the intrinsicoid deflection begins 0.06 second after the onset of QRS; V_3 and V_5 show this intrinsicoid deflection beginning 0.09 second after the onset of QRS. There appears to be a delay over both ventricles but the delay is greater over the left ventricle.

STUDIES

Typical Experiment.—The subject reclined on a comfortable bed and was attached to an electrocardiograph. The stethograph was used to register simultaneously with the electrocardiogram the orders "fast," "slow," and "relax." Fig. 2 is a typical experiment with control, "fast," and "slow" periods. The normally pronounced sinus arrhythmia almost disappears during cardiac acceleration. The measurement of cycle lengths and corresponding heart rates is given below the record. The orders "fast" and "slow" are easily seen in the sound track above the electrocardiogram. The resting control heart rate was 71 per minute. Exactly 1.60 seconds after the order "fast" the rate rose to 98, the fifth cycle rising to a rate of 120. The rate fell slightly (to 95) at the time the order "slow" was given. Just 1.12 seconds after the order "slow" the rate fell to 54 per minute. A pneumogram taken simultaneously showed that the respiratory rate increased up to 30 per minute and the respirations were very slight in depth. Table I is a summary of four of the experiments which serve as some of the controls.

Effect of Posture.—Vagus tone increases with the normal subject in the reclining position and decreases when the upright position is assumed.[13] Voluntary acceleration was performed in the two positions as shown in Table II. The standing rate increased over the dorsal rate. The average rate rose from 74 to 93 in the control observation. Acceleration occurred in the dorsal position in 1.56 seconds (average of four experiments). Acceleration in the standing position took place in 1.27 seconds, the rate increasing less because the control standing rate was faster. The rate after the order "fast" reached 121 faster than the rate in the reclining position. In summary, the lessening of vagus tone in the upright position did not have any significant influence on the acceleration mechanism.

Carotid Sinus Pressure Observations.—The effect of right and left carotid sinus pressure was studied in relation to the acceleration and deceleration of the heart. All the experiments were made with the subject in the recumbent position. Table III is a summary of the data. No slowing followed carotid sinus pressure. The acceleration was of the same degree as in the control experiments of Table I. The latent periods of acceleration and of deceleration were unchanged. Therefore, the influence of the vagus under the augmentation of carotid sinus pressure, both right and left, appeared to have no influence on the speeding up and slowing of the heart.

TABLE I. SUMMARY OF THE FINDINGS IN FOUR EXPERIMENTS. THESE CONTROL RESULTS ARE TO BE COMPARED WITH RESULTS THAT FOLLOWED VARIOUS PROCEDURES AND DRUGS

EXPERIMENT NUMBER	HEART RATE CONTROL	RATE AFTER ACCELERATION	MAXIMUM ACCELERATION	PER CENT ACCELERATION (AVERAGE)	LATENT PERIOD OF ACCELERATION (SEC.)	HEART RATE WITH SLOW	LATENT PERIOD OF SLOW (SEC.)	RESPIRATORY CONTROL	RESPIRATORY RATE AFTER ACCELERATION	RESPIRATORY RATE AFTER SLOW
1	71	98	107	38	1.68			24	29	Apneic
2	68	99	111	45	1.11	57	1.8	22	30	Apneic
3	68	96	107	41	1.40	60	1.8	22	29	Apneic
4	73	110	115	36	1.60	66	2.0	27	33	13

TABLE II. EXPERIMENTS OF EFFECT OF POSTURE ON VAGUS TONE

EXPERIMENT NUMBER	POSITION	CONTROL RATE	FAST RATE	SLOW RATE	CONTROL-TO-FAST (SEC.)	FAST-TO-SLOW (SEC.)	RELAX
1	Dorsal	72	118 + 46	100	1.48	1.50	
2	Dorsal	68	110 + 32	66	1.4	1.68	
3	Dorsal	81		72	Control to slow latent period not calculated		
4	Dorsal	71	114 + 43		1.64		On order "relax" rate: 71 in 1.12 seconds
5	Dorsal	78	104 + 26		1.60		On order "relax" rate: 80 in 1.92 seconds
6	Standing	83	122 + 39	69	1.60	1.21	
7	Standing	104	121 + 17	67	1.66	1.36	86
8	Standing	92	120 + 28		2.1		73 in 1.3 seconds
9	Standing	95		91	Latent periods not measurable		On "relax" rate: 94

TABLE III. EFFECTS OF CAROTID SINUS PRESSURE ON THE ABILITY TO VOLUNTARILY CONTROL HEART RATE

	HEART RATE CONTROL	RATE AFTER CAROTID SINUS PRESSURE	NET CHANGE	CAROTID SINUS PLUS "ACCELERATION"	PER CENT ACCELERATION	LATENT PERIOD OF ACCELERATION (SEC.)	HEART RATE "SLOW"	LATENT PERIOD OF "SLOW" (SEC.)
Right	75	81	+ 6	111 126	37	1.73	71	1.00
Right	63	69	+ 6	88	27	1.45	63	1.98
Left	57	56	− 1	83	48	1.20	53	1.67
Left	56	64	+ 8	92	44	1.41	53	1.53
Left	56	56	0	86	54	1.18	52	1.49

Respiration.—The electrocardiogram was taken simultaneously with the pneumograph attached to the chest and to the abdomen. Control respiration was 18 per minute and the heart rate was 67 per minute. Forced acceleration of respiration to 28 per minute increased the heart rate to 73 per minute. When the respiratory rate fell to 13, the heart rate was 98. In another experiment the respiratory rate was increased purposefully from 15 to 30 per minute. During the period of tachypnea the order "fast" was given and the heart rate increased from 65 to 104 per minute, and fell to 57 on the order "slow."

Changes in Intrathoracic Pressure.—In normal persons vagus tone varies with the phases of respiration, the heart rate increasing toward the end of inspiration (decrease in intrathoracic pressure) and slowing at the end of expiration (increase in intrathoracic pressure). With these facts in mind voluntary acceleration was performed under the conditions of Valsalva's experiment (forced expiration with the glottis closed) and Müller's experiment (forced inspiration with the glottis closed). (Table IV.)

TABLE IV. EFFECTS OF THE VALSALVA AND MULLER EXPERIMENTS UPON VOLUNTARY ACCELERATION

	HEART RATE			LATENT PERIOD	
	CONTROL	FAST	SLOW	CONTROL-TO-FAST (SEC.)	CONTROL-TO-SLOW (SEC.)
Valsalva's experiment (expiration)	69	105 + 36	95	2.92	1.97
Müller's experiment (inspiration)	75	112 + 37	76	2.71	1.55

Effect of Deep Inspiration and Breath-holding.—The subject inspired deeply and held his breath for ten seconds, at which time the order "fast" was given. The heart rate rose from 78 to 95 in 1.25 seconds. The rate rose later to 134. In 1.50 seconds after the order "slow," the rate fell to 77.

Duodenal Peristalsis and Voluntary Acceleration.—A small balloon inflated to a pressure of 5 mm. Hg was inserted in the duodenum (by fluoroscopic control) and the peristalsis studied. During the control period duodenal peristalsic waves occurred at a rate of 14 to 21 per minute. With voluntary acceleration the peristalsic waves persisted at the same rate.

Eye Changes (Observations by Dr. L. V. Johnson).—On inspection during the control period hippus was observed. With the order "fast" the pupil dilated slightly, the hippus persisting. There was slight pulsation of the retinal veins during "acceleration." Following the order "slow" the veins collapsed. Dilatation of the pupils persisted for a few minutes following acceleration.

Blood Pressure.—Observations of the blood pressure were made in the control experiments and in many of the others. The average control blood pressure was 128/70. With acceleration the pressure was 180 systolic and 94 diastolic. With deceleration the pressures fell to the control level.

Gastrointestinal Roentgenographic Studies.—The stomach and small intestines were observed after the ingestion of barium. No changes in peristalsis were noted during the period of acceleration. The barium passed through the small intestines at a normal rate. The examination was done by Dr. Carroll C. Dundon, to whom we are indebted.

Effort to Slow the Heart Without Previous Acceleration.—The subject attempted to slow his heart rate from the resting control rate. On several occasions when this was tried no change in heart rate occurred.

Electroencephalogram (We are indebted to Dr. C. T. Randt for these observations and interpretations).—A four channel amplifier and Grass ink-writing oscillograph were used to record brain and heart potentials. An electroencephalogram with both monopolar and bipolar tracings from occipital, postcentral, precentral, and frontal areas, with the reference electrode for monopolar recording attached to both ear lobes, was taken. There was no abnormality from either hemisphere, from homologous areas on both sides, or after two minutes and thirty seconds of hyperventilation. A dominant ten per second alpha rhythm was most prominent in occipital leads bilaterally.

Electrode placements on both upper arms with a three per cent gain, as opposed to twenty-five per cent gain for the brain potentials, were used to simultaneously record the electrocardiogram.

The electroencephalogram taken with the subject's eyes closed showed blocking of the alpha rhythm concomitant with the onset of voluntary acceleration of the heart rate. The alpha activity (10 per second) was suppressed, showing a decrease in amplitude and less frequent occurrence. Toward the end of each fifteen-second period of acceleration, the alpha rhythm again became more prominent. Similar blocking was observed on subsequent voluntary slowing of the heart rate with reappearance of alpha rhythm before the signal to relax was given.

Identical depression of the regular 10 per second waves was produced in the record by opening the eyes in a lighted room, by turning a flashlight beam on the subject's eyes, and by having him solve an arithmetical problem with his eyes closed.

In 1930, Berger[18] noted that any type of visual, auditory, or tactile stimulation which serves to attract the patient's attention tends to decrease the amplitude and occurrence of the alpha rhythm. The depression of the occipital alpha rhythm is probably a centrally determined response since it can be induced by hypnosis and attention.

The characteristic blocking response to attention was produced with voluntary acceleration of the heart rate.

Persistence of Acceleration.—An experiment to determine the ability of the subject to maintain sustained acceleration was performed. The control rate was 76; 1.12 seconds after the order "fast" was given the rate rose to 109 and in five cycles rose to 146, an increase of 70 beats per minute. He was able to maintain acceleration for one minute and fifty-five seconds, the rate falling to 84 at the end of the experiment. At this time the subject was exhausted and the experiment was stopped.

Heart Sounds.—The heart sounds were recorded simultaneously with the electrocardiogram. The first vibrations of the first heart sound occurred 0.08 second after the onset of QRS and at the apex of R (Fig. 3).

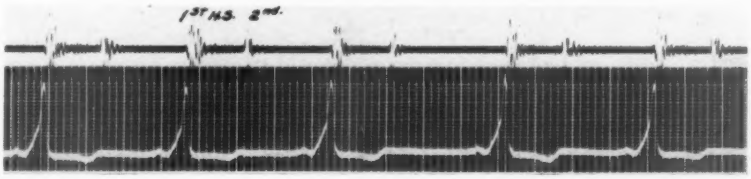

Fig. 3.—Simultaneous phonocardiogram and electrocardiogram. The first sound begins 0.08 second after the onset of the QRS complex.

Subclavian Pulse.—Optical records of the subclavian pulse were taken. During the period of acceleration the height of the waves was reduced, reflecting the reduced output per beat. There was no significant change in contour.

Peripheral Blood Flow.—Plethysmographic studies of the volume in the hands by Dr. A. S. Harris revealed a diminution during the period of acceleration. Control experiments with arithmetic problems failed to show a similar diminution. These studies suggest that sympathetic control is a prime factor in the speeding up of the heart. Similar results were reported in one of the earlier cases.[7]

Effect of Violent Exercise.—The subject climbed 100 steps rapidly and the respiratory rate increased to 35 per minute. The heart rate increased to 147 per minute. On the order "fast" the rate rose to 148 and on the order "slow" fell to 101 beats per minute. No abrupt change in rate occurred.

Adrenalin.—Adrenalin was injected subcutaneously (0.5 c.c., 1:1000 solution) after control studies. The data are seen in Table V. The usual subjective and objective symptoms, including a feeling of tension, palpitation, and body tremor, occurred. The heart rate rose to 112 per minute and the blood pressure to 150/80. Acceleration occurred following the order "fast" in about the usual time and to the same degree. The fastest rate was higher than in the control experiments. The slowing occurred in the usual interval although the rate was higher than in the control group.

Adrenalin augments the accelerator effect but does not prevent the ability of the subject to slow his heart quickly. It was decided to study the persistence

TABLE V. EFFECT OF ADRENALIN UPON ABILITY TO VOLUNTARILY CONTROL HEART RATE

	CONTROL	FAST	CONTROL-TO-FAST (SEC.)	SLOW	FAST-TO-SLOW (SEC.)	BLOOD PRESSURE	LAST OF FAST RATE	DURATION OF FAST RATE (SEC.)
Control	63	97	2.02	50	1.27	116/70		
Control	52	95	1.64	46	.91			
Control	56	87	2.24	58	2.34		72	74
4 minutes after adrenalin						150/80		
5½ minutes after adrenalin	63	90–123	2.16	87	2.13		119	103
16 minutes after adrenalin	73	107–120	1.52	84	1.50			
21 minutes after adrenalin	112	136	2.24	83	2.12	150/80		

of the tachycardia under control conditions and after adrenalin. The subject was requested to accelerate his heart and continue the fast rate as long as possible. He was able to maintain the increased rate for one minute and fourteen seconds. He was then ordered to slow his heart because of fatigue. Five and one-half minutes after 0.5 c.c. of adrenalin, he again was requested to speed his heart. This acceleration lasted one minute and thirty-eight seconds before fatigue caused us to order the subject to slow his heart. Numerous premature beats of ventricular origin caused trouble in measuring the latent period in some records. The data of the persistence experiment are summarized in Table VI.

Adrenalin augmented the subject's ability to speed the heart. He was able to continue the accelerated rate for a longer period, but he was still able to slow his heart quickly.

TABLE VI. RESULTS OF ATTEMPTS TO SUSTAIN ACCELERATION BEFORE AND AFTER ADRENALIN

	CONTROL RATE	FAST	CONTROL-TO-FAST	PERSISTENCE TIME	FASTEST RATE	FAST-TO-SLOW	RATE AT TIME OF SLOWING	SLOW
Control experiment	56	87	2.24 sec.	1 min., 14 sec.	98	2.34 sec.	68	54
After adrenalin	63	90	*	1 min., 38 sec.	123	1.85 sec.	110	87

*Cannot be measured because of premature beats.

Ergotamine Tartrate.—Ergotamine tartrate does not affect the sympathetic control of the heart,[14] but does slow the heart even after atropine. It also increases the excitability of the vagus to electric stimulation and to acetylcholine.[15] It slows sinus rhythm through direct action on the sinus node.[16] Ergotamine tartrate (0.5 mg.) was injected subcutaneously after a preliminary rest period and after control records were taken. A second dose of 0.5 mg. was given twenty-five minutes after the first injection. The results are summarized in Table VII.

In spite of the slowing effect on the control rates (74 to 47) the subject was still able to effect acceleration and to slow his heart in approximately the same intervals of time as before the injection of ergotamine. This suggests that the mechanism of acceleration was predominantly via sympathetic action.

Acetyl-beta-methylcholine.—The subject gave a history of asthma, so that two doses of 7.5 mg. were given (the second dose being given seven minutes after the first). Two minutes after the second dose the subject had flushing of the face, sweating, fullness of the head, salivation, and some dyspnea. Further use of choline was discontinued. The heart rate rose from 57 to 109 and the blood pressure from 130/66 to 148/50. The data of this experiment are given in Table VIII. No conclusions may be drawn from this experiment. The small dose was probably the cause of the increase in heart rate because of the action of the drug on the pacemaker.

TABLE VII. EFFECTS OF ERGOTAMINE TARTRATE ON THE ABILITY TO VOLUNTARILY CONTROL HEART RATE

	CONTROL	FAST	CONTROL-TO-FAST (SEC.)	SLOW	FAST-TO-SLOW (SEC.)	BLOOD PRESSURE
Control	74	111	1.72	58	.96	126 systolic
13 min. after 0.5 mg. ergotamine tartrate	60	100	1.70	59	1.52	126 systolic
15 min. after	50	92	1.57	51	1.84	
31 min. (0.5 mg., 2nd dose)	49	83	1.69	48	1.56	
43 min.	47	80	1.53	46	1.79	
45 min.	48	46		43		
		Rt. C.S.P.		C.S.P. off		
47 min.	47	44		45		
		Rt. C.S.P.		C.S.P. off		
51 min.	46	43		50		
		Lt. C.S.P.		C.S.P. off		
53 min.	44	49 F79	1.43	43 47	1.17	
		Lt. C.S.P.		C.S.P. off		
55 min.	48	53 78	2.02	45 51	1.45	
58 min.	44	46 78	1.64	44 42	.88	
		Rt. C.S.P.				
61 min.	46	48 79	.96	45 49	.72	

TABLE VIII. INFLUENCE OF ACETYL-BETA-METHYLCHOLINE ON ABILITY TO VOLUNTARILY CONTROL HEART RATE

	CONTROL	FAST	CONTROL-TO-FAST (SEC.)	SLOW	FAST-TO-SLOW (SEC.)	BLOOD PRESSURE
Control	57	96	2.10	83	1.20	130/66
5 mg. BMAC	109	159	2.80	112	1.98	148/50

Atropine.—Atropine has been used by a number of investigators to determine the effect of inhibition of the parasympathetic nervous system. Favill and White[6] showed that their subject could accelerate his heart even after atropine. A study of the effect of atropine was made in our case. Two mg. of atropine sulphate were injected hypodermically. The maximum effect occurred twenty-five minutes after the injection when his heart rate was 139 beats per minute. On the order "fast" the rate increased to 146, and within 10.2 seconds to 165. On the order "slow" the rate fell to 155, and then to 139. Later, two more efforts to accelerate the heart (with control rates of 135) were not followed by acceleration. Thus, it is seen that vagal inhibition may have played a part in the voluntary acceleration and slowing.

Amyl Nitrite.—Amyl nitrite was inhaled by the subject to determine the effect of cardiac acceleration and lowered diastolic blood pressure. Acceleration was attempted while inhaling amyl nitrite. The data are summarized in Table IX.

TABLE IX. INFLUENCE OF AMYL NITRITE UPON VOLUNTARY CONTROL OF HEART RATE

	CONTROL	FAST	CONTROL-TO-FAST (SEC.)	SLOW	FAST-TO-SLOW (SEC.)	RELAX*
Control	69	125	1.34	63	1.21	
Amyl nitrite	76	129				
Amyl nitrite	83	125	1.28	170		136

*Subject requested to relax.

Inhalation of amyl nitrite resulted in moderate tachycardia in the control observation. When voluntary acceleration was attempted the heart rate rose from 83 to 125 and later to 157. When told to "slow" the heart, the rate increased from 157 to 170, gradually. When told to "relax" the rate gradually fell to 136. Thus, voluntary acceleration probably was moderately effective immediately; but the rate rose to 157 subsequently. When told to "slow," the heart rate was not under control of the will because of the reflex from the carotid sinus and also because of reflex depression of the vagus center.[17] Amyl nitrite did not abolish the abnormal ventricular complexes.

Digitalis.—The effect of digitalis was studied because of its profound action on the vagus nerve and on the heart muscle. The subject was given 1.8 Gm. of digitalis powder in 24 hours and studied. Digitalization did not abolish the anomalous excitation of the ventricles. The results of this experiment are given in Table X.

TABLE X. DIGITALIS AND VOLUNTARY ACCELERATION

CONTROL	FAST	CONTROL-TO-FAST (SEC.)	SLOW	FAST-TO-SLOW (SEC.)
52	79	1.74	45	1.54

The increase in heart rate after "fast" was 27 beats, or 52 per cent; proportionally as great as in the control experiments. The responses to "slow" were equally effective and fast. Vagal influence does not interfere with the acceleration mechanism, with the subject digitalized.

Quinidine.—Quinidine has been reported as effective in abolishing the anomalous conduction.[12] The administration of 2 Gm. of quinidine sulphate did restore normal conduction as illustrated in Fig. 4.

Again augmentation of the vagus effect did not prevent acceleration of the heart to the usual degree. (Table XI.)

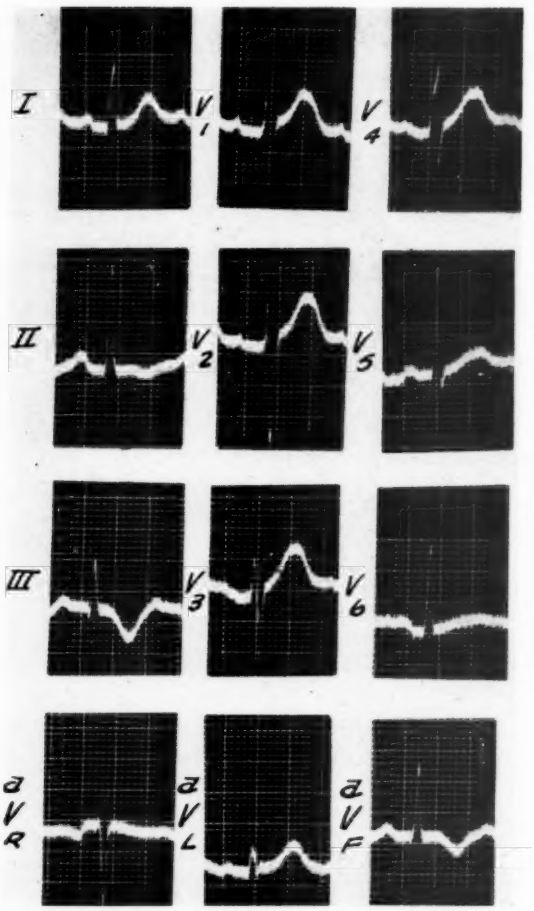

Fig. 4.—Restoration of normal conduction by quinidine.

TABLE XI. QUINIDINE AND VOLUNTARY ACCELERATION

	CONTROL	FAST	CONTROL-TO-FAST (SEC.)	SLOW	FAST-TO-SLOW (SEC.)	ECG
Control	55	85	1.73	46	1.57	W. W. P. S.
2 Gm. quinidine	105	120	2.36	101	2.44	N. M.
24 hrs. later	67	91	1.36	55	1.22	W. W. P. S.

DISCUSSION

The evidence suggests that the voluntary acceleration is due preponderantly to sympathetic action. Acceleration occurred after adrenalin, as well as after atropine, but the increase was greater after adrenalin. The acceleration was definite twenty-five minutes after atropine, but later the control rate of 135 was not increased by the order "fast." This may have been due to fatigue, as the subject had noted previously that his facility to voluntary acceleration decreased with repeated trials. The voluntary slowing after acceleration was not altered by atropine (in the early experiments) or by adrenalin. The inhalation of amyl nitrite did not prevent voluntary acceleration, but the progressive increase in heart rate on the order "slow" may have been the result of the amyl nitrite. The fact that drugs increasing vagus effect (ergotamine, digitalis, and quinidine) do not alter the ability of the subject to speed up and slow his heart suggests that vagus action may be in part involved. This is in keeping with the idea that cardiac function results from the balance between the activities of the sympathetic and the parasympathetic divisions of the autonomic system. The evidence of the electroencephalogram shows that the subject did have cerebral activity preceding the acceleration, as in any thought process.

CONCLUSIONS

1. This twenty-first reported case of voluntary acceleration and deceleration of the heart is unique in its association with anomalous ventricular excitation (Wolff-Parkinson-White syndrome).

2. Adrenalin and atropine given in physiologic doses do not prevent the ability of the subject to control his heart action. Adrenalin appears to have an augmenting effect on acceleration.

3. Drugs increasing vagus tone (digitalis, quinidine, and ergotamine tartrate) do not prevent the acceleration and deceleration.

4. No physical means of acceleration (changes in respiration or muscular activity) were demonstrated.

5. The electroencephalogram demonstrated that psychic activity preceded the acceleration.

6. The diminution in the peripheral blood flow and the dilation of the pupils further substantiate the importance of the impulses via the sympathetic system.

7. The ability of the subject to influence his heart rate was chiefly through sympathetic control, but inhibition and augmentation of vagus influence also played a part.

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SUBACUTE BACTERIAL ENDOCARDITIS OF UNDETERMINED ETIOLOGY

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OF A current series of 166 patients with subacute bacterial endocarditis, we have encountered eleven (7 per cent) with consistently sterile blood cultures despite recourse to anaerobic methods, enriched mediums, arterial punctures, and cultures taken after the administration of epinephrine.* The diagnosis in two of our patients was confirmed by necropsy findings. In the remainder, the recognition of the presence of the syndrome was dependent upon the classical manifestations of protracted fever, valvulitis, embolic phenomena, and usually a splenomegaly. Needless to say, the other possible etiological factors in a prolonged pyrexia were excluded by extensive laboratory investigations.

This communication has for its purpose a summation of eleven histories, a report of the responses to therapy, and the suggestion that the response to treatment with anti-infective agents be employed in the future as a therapeutic test.

CASE REPORTS

CASE 1.—Subacute bacterial endocarditis, eighteen months: primary rheumatic cardiovalvular lesion of mitral and tricuspid valves; no response to fourteen days of penicillin-heparin therapy.[1-7] Necropsy findings: thromboulcerative mitral endocarditis, healed rheumatic endocarditis of mitral and tricuspid valves, multiple infarcts, avitaminosis, and cachexia; cultures of valves sterile, colonies of organisms in histopathologic section of valves.

C. M. T., a 48-year-old white man, was known to have had a heart murmur since early childhood, with no actual diagnosis of rheumatic fever or scarlatina. He entered the Jewish Hospital of Brooklyn on July 6, 1944, complaining of chills, fever, weakness, loss of weight, nausea, and petechiasis. Eighteen months prior to the onset of this illness he had "flu" which lasted for about three days. The fingers became clubbed and he developed splenomegaly. During the past twelve months he lost approximately forty pounds in weight.

On examination he was found to be an emaciated, chronically ill man who was very pale, with a suggestive cafe-au-lait complexion. There was a presystolic rumble at the apex and a systolic murmur heard over the entire precordial area. The blood pressure was 90/46. The spleen was palpable 5 cm. below the costal margins. The liver was enlarged to 7 cm. below the costal margins. There was clubbing of the fingers.

The clinical impression was subacute bacterial endocarditis engrafted on a rheumatic heart lesion. X-ray examination revealed considerable enlargement of the heart with aortic and mitral

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*Epinephrine technique for obtaining positive blood cultures was originally suggested by Dr. Myron Prinzmetal and Dr. B. S. Oppenheimer.

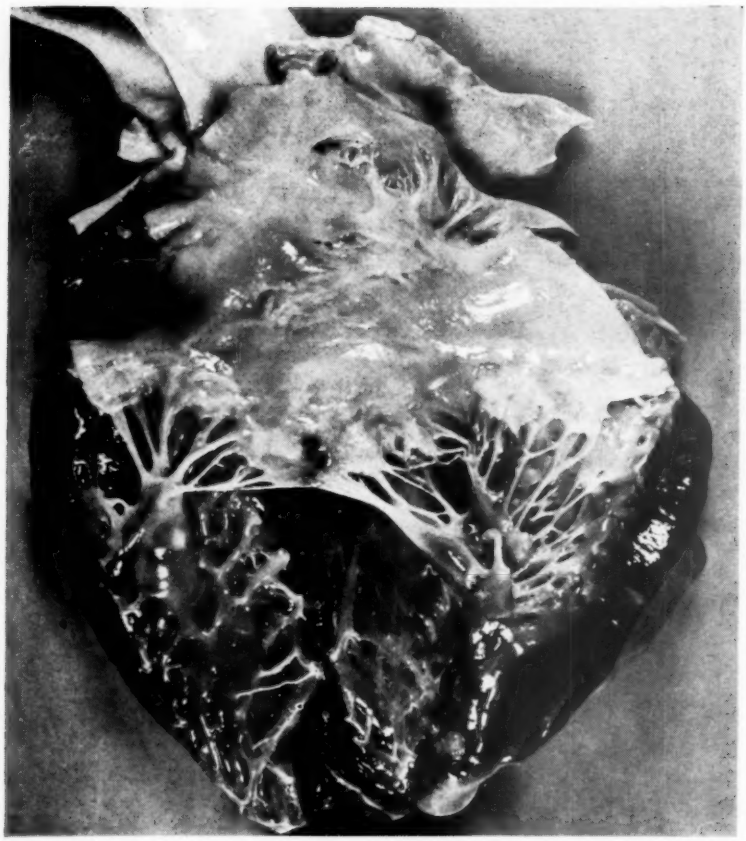

Fig. 1.—Case 1. Endocarditis of mitral valve.

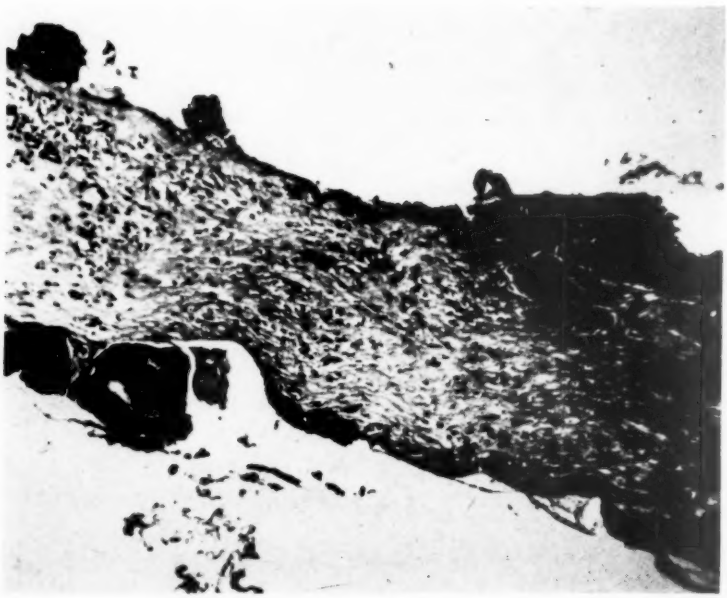

Fig. 2.—Case 1. Photomicrograph of mitral valve with vegetation. H. and E., × 8.

configuration. Electrocardiogram was negative, except for a low T_1. The urinalysis showed albumin, occasional white blood cells, red blood cells, and epithelial cells.

In spite of the sterile blood cultures it was felt that this was nevertheless an advanced case of subacute bacterial endocarditis, and he was started on combined penicillin-heparin therapy. He received a total of 4,900,000 Oxford units of penicillin and 1,350 mg. of heparin over a period of twenty-two days. He was also given digitalis and ammonium chloride because of the advanced myocardial and renal decompensation. Fourteen days after penicillin therapy was started, during which time his condition rapidly deteriorated to the point of cachexia, the patient suddenly went into shock, and despite the administration of two units of human blood plasma, died. During his entire stay at the Jewish Hospital of Brooklyn he had frequent blood cultures, all of which were sterile.

At necropsy* the patient was found to have a thromboulcerative mitral endocarditis; a healed rheumatic endocarditis of the mitral and tricuspid valves (Figs. 1 and 2); a thrombus in the right auricle numerous splenic infarcts (Fig. 3); and infarcts of the kidney, interstitial nephritis, nephrosis, and glomerulitis (Figs. 4 and 5) with adenoma of the left kidney. The myocardium was red-brown in color with grey streaking and was studded with Bracht-Wachter bodies (Fig. 6). He also had erosions of the stomach, urinary bladder, and esophagus, indicative of nutritional insufficiency and avitaminosis. There was also marked generalized emaciation. Cultures taken of all the heart valves were sterile despite the fact that histopathologic section of the affected valves disclosed colonies of organisms in the depths of the vegetations.

CASE 2.—Subacute bacterial endocarditis, recovery with one five-week span of combined penicillin-heparin treatment; post-therapy, nineteen months. Primary rheumatic cardiovalvular lesion of mitral valve.

A. R., a 41-year-old white man, entered the Jewish Hospital of Brooklyn on Oct. 23, 1944, complaining of dyspnea on exertion. He was well until four years prior to admission when he began to complain of temperature, chills, weakness, and fatigue. One year later he had arthralgia of the left knee which was satisfactorily treated with fever therapy and salicylates, but thereafter he ran a very low temperature for four weeks. One year later he had a similar episode affecting the right knee. One year after that he suffered a coronary thrombosis and was in bed for six weeks, following which he had precordial pressure for three to six months. For the ensuing year he had occasional episodes of fever which responded well to sulfamerazine. Six months prior to admission he awoke suddenly complaining of severe pain in the left eye and a petechia was noted on the conjunctival surface.

On admission he was found to be a well-developed, well-nourished white man, who did not appear acutely ill. Examination of the cardiovascular system revealed a regular sinus rhythm with an accentuated apical thrill. There was a systolic murmur and a short presystolic rumble at the apex, especially after exertion, and best heard while lying in the left lateral position. Extremities revealed minimal clubbing of the fingers with subungual splinter hemorrhages.

The electrocardiogram was suggestive of myocardial damage. Repeated blood cultures were sterile, but *Streptococcus viridans* was isolated from the root of an extracted tooth. Despite the protracted history and the persistently sterile blood cultures a diagnosis of subacute bacterial endocarditis was justified because of the cardiac lesion, the temperature, and subungual hemorrhages. He was placed on penicillin and heparin therapy and received a total of 23,700,000 Oxford units of penicillin in dosages varying from 300,000 to 1,000,000 units daily, for a period of five weeks. Four weeks after the beginning of therapy he developed an embolism of the terminal branch of the dorsal arch, analagous to an Osler node, which was painful and very tender. This responded promptly to subcutaneous implants of heparin in the Pitkin menstruum. Upon discharge from the hospital his general condition was excellent; he had no complaints, the cardiac murmurs were less apparent, and there was no splenomegaly. The erythrocyte sedimentation rate was within normal limits. Nineteen months after discharge from the hospital his condition is still excellent and he is able to carry on his customary duties.

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*We are indebted to Dr. David M. Grayzel, Acting Director of the Department of Pathology, Jewish Hospital of Brooklyn, for supplying the pathologic data.

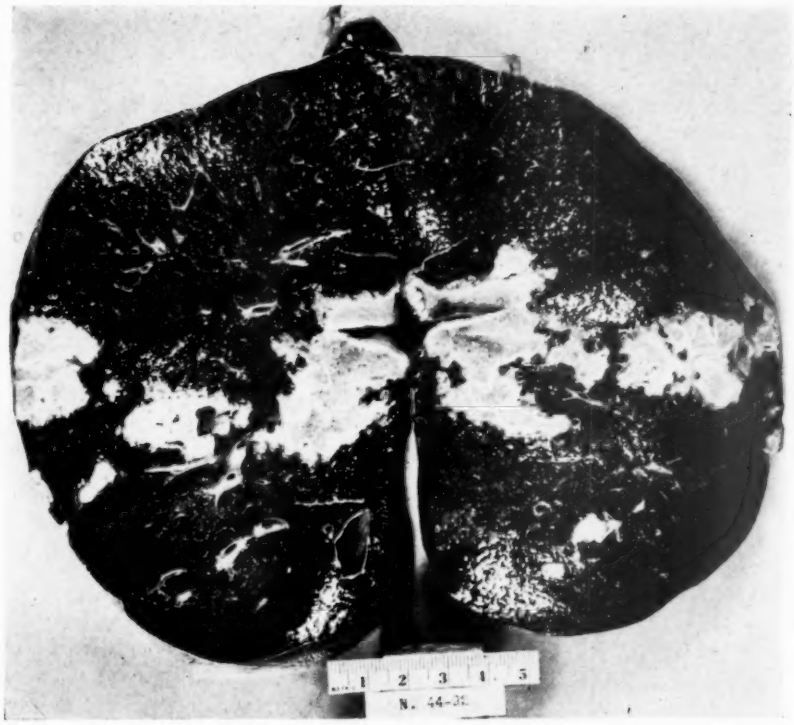

Fig. 3.—Case 1. Cut surface of spleen showing infarcts.

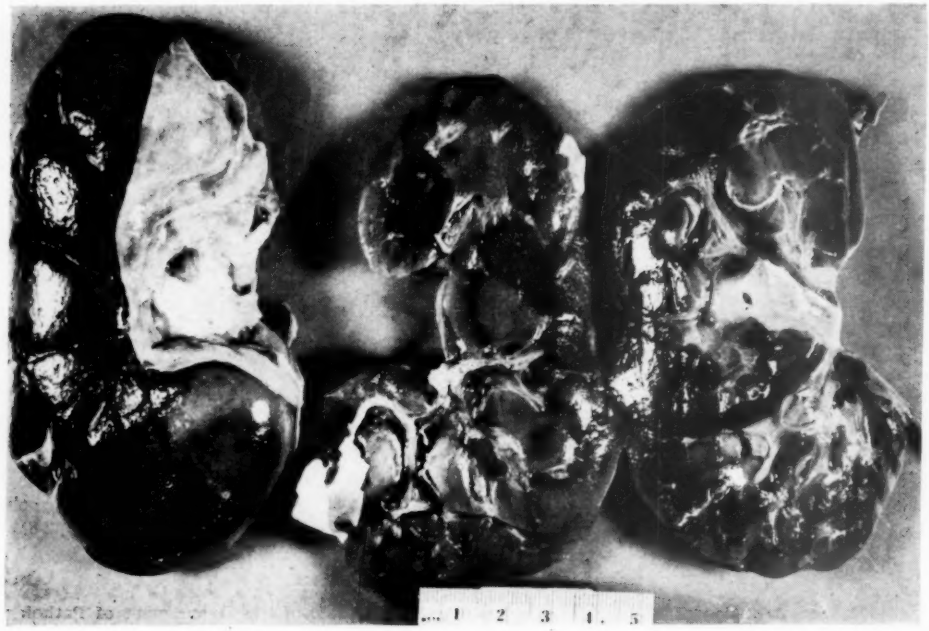

Fig. 4.—Case 1. Photograph of kidney showing infarcts.

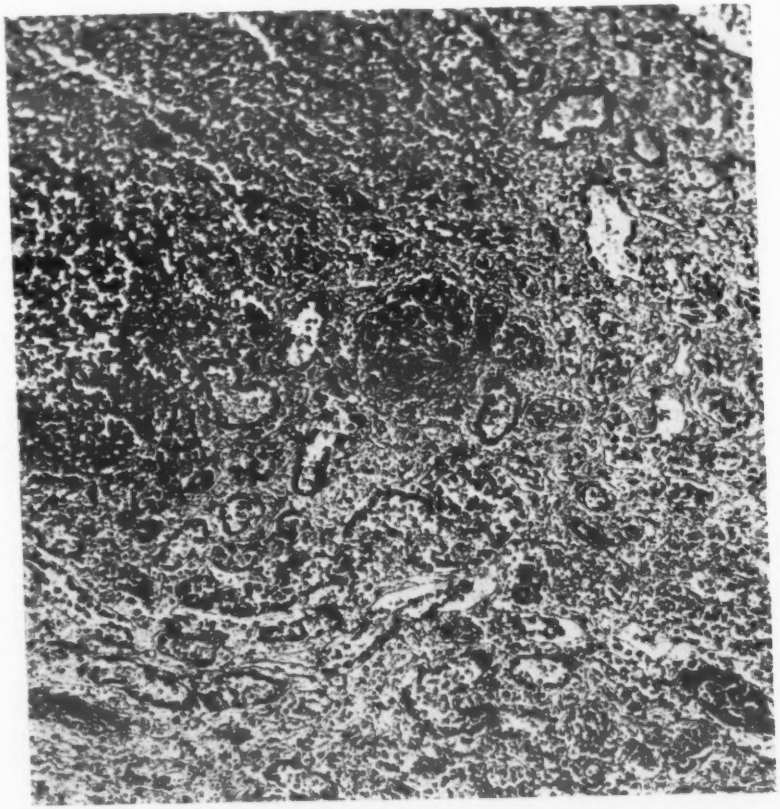

Fig. 5.

Fig. 5.—Case 1. Photomicrograph showing infarct in kidney. H. and E., × 220.

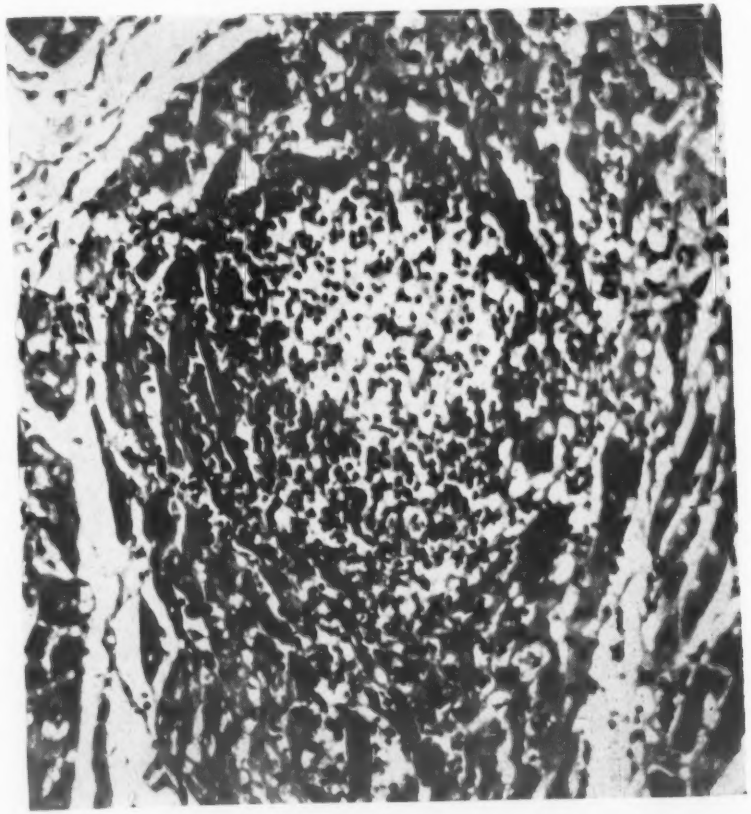

Fig. 6.

Fig. 6.—Case 1. Photomicrograph showing Bracht-Wachter body. H. and E., × 210.

CASE 3.—Subacute bacterial endocarditis, two and one-half months; primary rheumatic cardiovalvular disease of mitral and aortic valves; no response to one three-week course of penicillin intramuscularly; recovery following thirty-six-day span of combined penicillin-heparin therapy: post-therapy, nineteen months.

S. F., a 28-year-old white woman, had temperature and malaise for a period of two and one-half months. At another hospital a diagnosis of subacute bacterial endocarditis was made and she was given penicillin alone intramuscularly for three weeks and then discharged. Five blood cultures taken at that institution were sterile. After five symptomless weeks she again became febrile and was admitted to the Jewish Hospital two days later, on Nov. 21, 1944. There was no past history of any cardiac lesion or rheumatic fever. Cardiac examination disclosed a forceful thrust with systolic thrill and rough systolic murmur at the apex, and a high-pitched, blowing systolic murmur at the aortic area. Splenomegaly and hepatomegaly were present. There was slight cyanosis of the nails with clubbing. No petechiae were observed. The clinical impression was subacute bacterial endocarditis superimposed on rheumatic disease of the mitral and aortic valves. The electrocardiogram disclosed some myocardial damage. All urine specimens showed a faint trace of albumin. All blood cultures were sterile. The patient was given a total of 22,900,000 Oxford units of penicillin and 2,300 mg. of heparin intravenously over a period of thirty-six days, with daily dosages of penicillin ranging from 300,000 to 1,000,000 Oxford units. Nineteen months after discharge patient is well, symptom-free, afebrile, and has returned to her former occupation as a secretary.

CASE 4.—Subacute bacterial endocarditis, four months; primary rheumatic cardiovalvular disease of mitral and aortic valves; infection terminated by two courses of combined penicillin and heparin treatment, twenty-two and thirty-five days respectively; patient succumbed to intractable congestive heart failure. Necropsy showed healed thromboulcerative endocarditic lesions of mutilated aortic and mitral valves; cultures sterile and histopathologic sections negative for bacteria.

S. McF., a 50-year-old white man, entered the Jewish Hospital of Brooklyn on March 22, 1945, complaining of cough and fatigue. Four months prior to admission he had two upper respiratory infections within a three-week period. One month later he had swelling and pain of both ankles and knees, but there was no redness or heat. This was followed by a nonproductive cough and pain in the lumbar region. Two months later he became very easily fatigued and had noticeable loss of strength. This was accompanied by some frequency of urination and precordial pain with palpitation. Two weeks prior to admission he developed a low grade temperature ranging between 100° F. and 102° F., with the peaks occurring at night. He gave no history of rheumatic fever or scarlatina.

On examination he was a well-developed, well-nourished white man who did not appear acutely ill. The heart was enlarged to the left. There was a soft systolic and diastolic murmur over the entire precordial area, radiating to the left axilla and upward to the neck. The rhythm was regular and the blood pressure was 118/100. There was hepatomegaly but no splenomegaly. The fingers were clubbed. Electrocardiogram showed evidence of myocardial damage. Teleroentgenogram demonstrated a mitralized heart with aortic changes. In spite of the fact that repeated blood cultures were sterile, it was felt that this was a case of subacute bacterial endocarditis engrafted on an old rheumatic valvular defect (mitral and aortic) and combined penicillin-heparin therapy was started. He received an initial course of 2,000,000 Oxford units of penicillin daily, totalling 44,000,000 Oxford units and 2,400 mg. of heparin administered in the Pitkin menstruum for a period of twenty-two days. During this first course of therapy the patient reacted fairly well. However, because of a persistently elevated erythrocyte sedimentation rate it was decided to give a second five-week span of combined therapy, totalling 68,000,000 Oxford units of penicillin and 700 mg. of heparin. Five weeks after this therapy he developed dyspnea and orthopnea and the spleen enlarged to 3 cm. below the costal margin. The heart sounds over the entire precordial area were replaced by a systolic and diastolic murmur, and he developed congestive heart failure of both the backward and forward type. His condition rapidly deteriorated and electrocardiographic studies showed the development of an intraventricular conduction disturbance, with severe myocardial damage and the common type of bundle

branch block. In spite of digitalization and the usual therapeutic measures, the patient died sixteen weeks after admission.

Necropsy, limited to examination of the heart, showed healed thromboulcerative endocarditic lesions of the mitral and aortic valves, the later being bicuspid. The vegetations of the mitral valve were endothelialized and very firm. The chordae tendineae of the mitral valve were thickened and fused. There was also a healed rheumatic endocarditis of this valve (Fig. 7). The aortic valve leaflets were markedly fragmented, the free borders of the valve were frayed, the fragments extending down to the left ventricle (Fig. 8). Cultures of the heart valves were sterile and histopathologic sections of all valves failed to disclose any bacteria. The heart was hypertrophied and markedly dilated. It was apparent that the intractable heart failure was predicated on inability of the heart muscle to accommodate for the severe mutilation of the valves despite the fact that the treatment succeeded in sterilizing the endocarditic lesions.

CASE 5.—Subacute bacterial endocarditis, eleven days; primary congenital heart disease, patent ductus arteriosus; no response to penicillin by fractional intramuscular route; recovery following sixty-six day span of penicillin-heparin treatment; post-therapy, thirteen months.

J. L., a 35-year old white woman, was admitted to the Jewish Hospital of Brooklyn on April 15, 1945, complaining of lower abdominal discomfort, fever, headaches, and ocular pain of eleven days' duration. At the age of three she had had diphtheria, following which her family was informed that she had heart disease. There was no past history of rheumatic infection, scarlet fever, or chorea. On admission, she appeared to be well developed, well nourished, and not in acute distress. Her temperature was 101° F., pulse rate 114 per minute, and blood pressure, 130/70. The cardiac findings were characteristic of patent ductus arteriosus which was confirmed radiographically. There was bilateral costovertebral jar tenderness. There was no splenomegaly or hepatomegaly. The electrocardiogram revealed left ventricular preponderance and myocardial damage. The erythrocyte sedimentation rate was 122 mm. in one hour (Westergren) and the urine showed traces of albumin and the presence of red blood cells. Despite the consistently sterile blood cultures, the clinical impression was subacute bacterial endocarditis engrafted on a patent ductus arteriosus with embolization to the kidneys. The patient was placed on a treatment program consisting first of sulfonamides and then of penicillin given by the fractional intramuscular method. Her condition became progressively worse, the presenting clinical feature being repeated pulmonary embolization with consequent massive infarction and consolidation. She was then referred for intensive therapy which was begun with a dosage plan of 500,000 Oxford units of penicillin and 100 mg. of heparin by continuous venoclysis. It was not, however, until the daily penicillin dose was increased first to 2,000,000, then to 5,000,000, and finally to 10,000,000 Oxford units that the response was satisfactory and the infection controlled. After a rather stormy course, during which time the patient received a total of 215,000,000 Oxford units of penicillin and 2,500 mg. of heparin over a period of sixty-six days, the clinical condition improved considerably, the symptoms disappeared, temperature became normal, and the erythrocyte sedimentation rate receded to 19 mm. in one hour. She was discharged from the hospital on Oct. 21, 1945, and is now completely recovered and carrying on with her activities as housewife.

CASE 6.—Subacute bacterial endocarditis, five months; primary rheumatic cardiovalvular disease of mitral and aortic valves; infection terminated by one twenty-two-day span of penicillin-heparin therapy; succumbed to coronary artery thrombosis nine months post-therapy.

A. S., a 42-year-old white man, was admitted to the Jewish Hospital of Brooklyn on June 25, 1945, complaining of migratory polyarthritis and low grade temperature for a period of five months. The pyrexial periods were preceded by chilly sensations, but no actual shaking chills. The skin presented transitory crops of painful lesions (embolic), lasting from twenty-four to thirty-six hours. One week prior to admission, he developed a nonproductive cough. There was no past cardiac history.

On admission he was found to be an acutely ill man with marked pallor. The teeth were in poor dental condition. He had a sinus tachycardia and a Corrigan pulse. The heart was enlarged to the left and to the right. The first sound at the base was replaced by a loud systolic

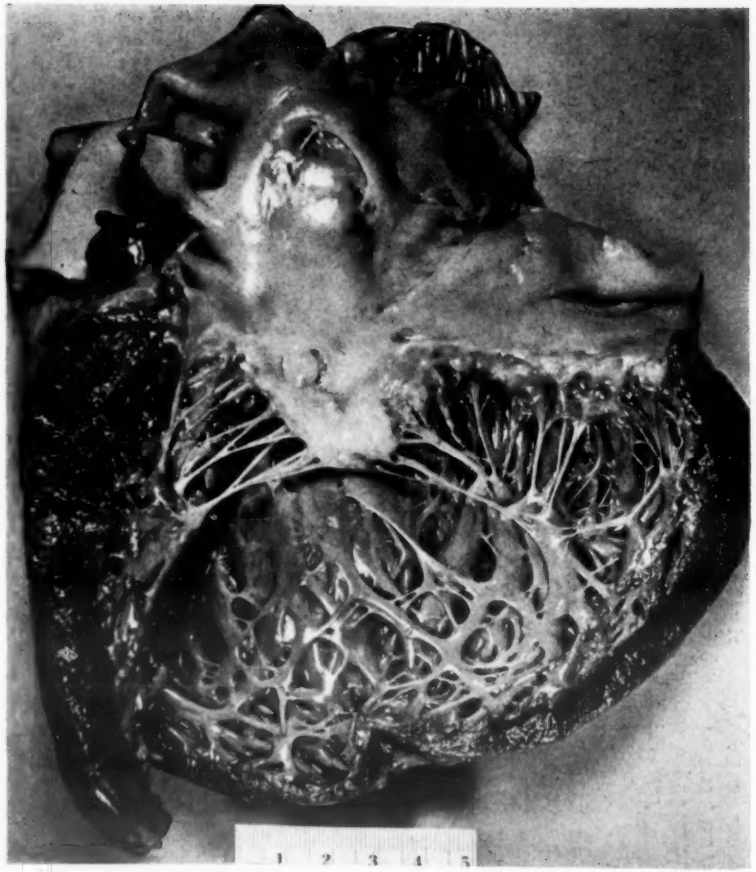

Fig. 7.—Case 4. Endocarditis of mitral valve. Note thickening of valve cusps and chordae tendineae.

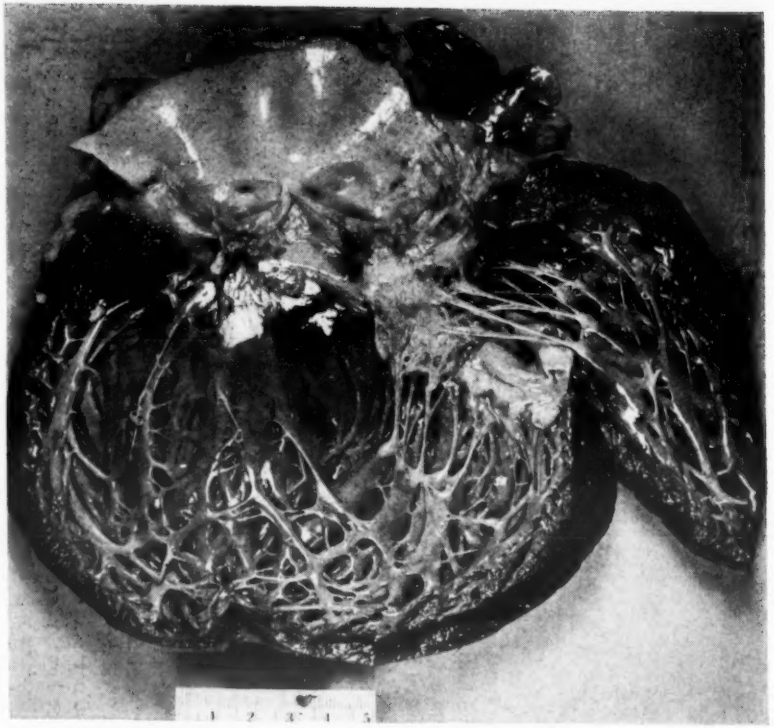

Fig. 8.—Case 4. Endocarditis of aortic valve.

murmur, best heard at Erb's point. The liver was enlarged 5 cm. below the costal margin and the edge was tender. Splenomegaly measured 3 cm. below the costal margin. There was marked bilateral clubbing of the fingers. The left ankle was markedly tender, red, and swollen. Petechiae were present on the left large toe and on the medial aspect of the left heel. The clinical impression was polyarthritis, aortic insufficiency, and aortic stenosis, with mild congestive failure, and superimposed subacute bacterial endocarditis. Blood cultures taken for three consecutive days and weekly thereafter were sterile. Electrocardiogram revealed myocardial damage and a prolongation of the P-R interval to 0.32 second. The hemogram showed 58 per cent hemoglobin, 3.11 million red blood cells, 8,400 white blood cells with 75 per cent polymorphonuclear leucocytes, 18 per cent lymophocytes, and 7 per cent monocytes.

Because of the poor condition of the patient, and despite the sterile blood cultures, he was placed on massive penicillin-heparin therapy. During the course of treatment he had petechiasis of the right foot, a right renal infarct, and right saphenous vein thrombophlebitis. The latter two were cleared up without residue by subcutaneous injections of heparin in the Pitkin menstruum. After twenty-two days of treatment, using 500,000 Oxford units of penicillin daily intravenously and totaling 11,000,000 Oxford units, the patient became afebrile, asymptomatic, and ambulatory.

The patient remained well for nine months when he was readmitted to the hospital in acute heart failure with pulmonary edema. This developed suddenly on the evening of admission. The acute heart failure was probably due, as evidenced by the electrocardiogram, to early posterior wall infarction superimposed on an old anterior wall infarction. There was no indication of any recurrent bacterial endocarditis. The patient died suddenly seven days after admission. No autopsy was obtained. The final diagnoses were (1) acute left ventricular failure with pulmonary edema (coronary occlusion), (2) rheumatic heart disease, and (3) healed subacute bacterial endocarditis.

CASE 7.—Subacute bacterial endocarditis, two months; primary atherosclerotic cardiovascular disease; successful response to thirty-five-day span of penicillin-heparin treatment; post-therapy, eight months.

M. S., a 48-year-old white man, was admitted to the Jewish Hospital of Brooklyn on Aug. 8, 1945, complaining of migratory polyarthritis which had been present for a period of two months. Five weeks prior to admission he developed a sore throat with temperature and was treated with sulfonamides and penicillin. For the previous three weeks he had a continuous low grade temperature, increasing fatigability, and loss of weight.

Examination revealed a well-developed, well-nourished white man who did not appear acutely ill. The clinical findings justified a diagnosis of subacute bacterial endocarditis superimposed on an atherosclerotic cardiovascular lesion. He had minimal clubbing of the fingers. Blood pressure was 120/92. Teleroentgenogram revealed left ventricular enlargement; and the electrocardiogram, left axis deviation. The erythrocyte sedimentation rate was 67 mm. in one hour (Westergren) and urinalyses showed faint traces of albumin and occasional white blood cells. Repeated blood cultures were sterile. He was started on 500,000 Oxford units of penicillin daily by vein, with heparin, and given a thirty-five-day span of treatment totaling 17,500,000 Oxford units of penicillin and 2,700 mg. of heparin. He responded promptly, became progressively better, and although the sedimentation rate remained slightly elevated, he was discharged from the hospital as a recovered case.

CASE 8.—Subacute bacterial endocarditis, four months; primary rheumatic cardiovalvular disease of the mitral valve; unsuccessful response to prolonged, intensive, massive penicillin-heparin therapy; recovery following forty-six days of streptomycin; post-therapy, eight months.

E. L. S., a 25-year-old white woman, was well until four years prior to her present illness. At that time she was told that she had a "bad heart" (rheumatic heart disease). Four months prior to admission, following an upper respiratory infection, the patient developed a persistent fever associated with chills, malaise, and pallor. Numerous blood cultures, aerobic and anaerobic, were consistently sterile. Six days after admission to another hospital, on Aug. 30, 1945, she developed splenomegaly and began to deteriorate. The temperature ranged between 103° F.

and 105° F. and the clinical picture seemed typical of subacute bacterial endocarditis. The patient, therefore, was started on penicillin-heparin therapy and after four days the temperature characteristically dropped and she improved greatly. However, despite intensification of the therapy, the temperature recurred and her condition rapidly became worse. She was then transferred to the Jewish Hospital of Brooklyn where after a comprehensive clinical and laboratory survey all alternative diagnoses were again excluded. The daily dosage plan of penicillin was stepped up to five million Oxford units and then to ten million Oxford units without significant response. Repeated blood cultures were sterile. The temperature continued to spike and the hemic component remained low in spite of numerous blood transfusions. On the one hundred thirtieth day of her illness, the spleen became markedly enlarged and although splenic and sternal marrow punctures were negative, the possibility of Hodgkin's disease was considered. Probationary x-ray therapy was instituted but was discontinued because of the failure of response. Penicillin therapy was again started, using 10,000,000 Oxford units daily with heparin. Her clinical condition continued to regress to such an extent that she lost approximately 60 pounds in weight, had complete anorexia, and death was expected momentarily. On the one hundred sixtieth day of her illness, streptomycin therapy was added to the program. It was given intramuscularly because of the presence of pyrogens which contraindicated its intravenous use. Forty-eight hours after streptomycin therapy was begun the temperature receded to 101° F., her appetite increased, and her general condition improved remarkably. It was decided to continue with streptomycin alone. During the forty-six days of streptomycin therapy, a total of 57.5 Gm. (57,500,000 units) were given in dosages ranging from 1 to 2 Gm. daily. While on this therapy, the appetite increased greatly and the patient gained some 35 pounds in weight. She is now eight months post-therapy, completely afebrile, and ambulatory. She now weighs 150 pounds, which represents a total gain of 40 pounds, the hemoglobin is 82 per cent, and the erythrocyte sedimentation rate is 7 mm., as contrasted with a high of 117 mm. in one hour (Westergren) during the active illness.

CASE 9.—Subacute bacterial endocarditis, one year; primary rheumatic cardiovalvular disease of the mitral valve; two courses of penicillin alone of twenty-one and forty days, respectively, failed to terminate the infection; successful response to one fifty-three-day span of combined penicillin-heparin treatment; post-therapy, four months.

L. G., a 44-year-old white woman, who was admitted to the Jewish Hospital of Brooklyn on April 9, 1946, had developed intermittent and irregular temperature one year prior to admission. The temperature, cardiac lesion, splenomegaly, and petechiasis of the fingers justified a diagnosis of subacute bacterial endocarditis superimposed on a rheumatic cardiovalvular defect (mitral stenosis). Despite the repeatedly sterile blood cultures, in May, 1945, at another institution, she received a three-week span of treatment with penicillin by fractional intramuscular method totalling 3,675,000 Oxford units. This therapy resulted in the disappearance of all symptoms. Her symptoms returned and the patient was retreated in June, 1945, receiving a total of 54,400,000 Oxford units intramuscularly over a period of forty days. She was discharged afebrile and improved, though with persistent splenomegaly.

On admission to the Jewish Hospital, she appeared well developed, well nourished but pallid, and chronically ill. Cardiac findings indicated a double mitral lesion which was confirmed radiographically. Hepatomegaly and splenomegaly were 5 cm. and 3 cm., respectively, below the costal margin. Blood pressure was 130/80. Electrocardiogram showed simple P-R prolongation and myocardial damage. Repeated blood cultures were sterile. Erythrocyte sedimentation rate was 118 mm. in one hour (Westergren) and the urine contained occasional white and red blood cells.

She became afebrile on combined penicillin and heparin treatment. The secondary anemia was combatted with repeated blood transfusions and hematinics. The total penicillin given was 228,000,000 Oxford units over a period of fifty-three days, with a total of 3,800 mg. of heparin. At the completion of this therapy, while ambulatory, the patient developed thrombophlebitis of the left lower extremity which responded to seven deposits of heparin, given in the Pitkin menstruum over a period of fourteen days, and totalling 2,300 milligrams. She is now four months post-therapy and continues to fulfill the criteria of a recovered case.

CASE 10.—Subacute bacterial endocarditis, six weeks; primary rheumatic cardiovalvular disease of the mitral valve; recovery following one forty-one-day span of combined penicillin-heparin treatment; post-therapy, four months.

L. R., a 20-year-old white man, was admitted to the Jewish Hospital of Brooklyn on April 19, 1946. He had had rheumatic heart disease at the age of 2 years but remained well until six weeks prior to admission. Since then he had recurrent temperature with and without chills, aching joints, and sore spots in various sites.

On admission the important cardiac finding was a blowing systolic murmur at the apex referred all over the precordium. Hepatomegaly was 2 cm. below the costal margin. Blood pressure was 125/80. Electrocardiogram disclosed mild myocardial damage. Erythrocyte sedimentation rate was 15 mm. in one hour. (Patient had had some penicillin treatment before admission to the hospital.) The blood cultures were all sterile. The diagnosis was subacute bacterial endocarditis engrafted on a rheumatic valvular defect and intensive penicillin-heparin therapy was begun. Because of the preadmission subcurative penicillin therapy, a minimum daily dosage of 2,000,000 Oxford units was indicated. Due to lack of prompt response, this was immediately increased to 5,000,000 units. He was given a total of 182,000,000 units in forty-one days, with a total of 2,500 mg. of heparin. He is now four months post-therapy and is considered a recovered case.

CASE 11.—Subacute bacterial endocarditis, five months; primary rheumatic cardiovalvular disease of the mitral valve; cerebral embolus; recovery following one thirty-six-day span of combined penicillin-heparin treatment; post-therapy, four months.

H. W., a 51-year-old white woman, was admitted to the Jewish Hospital of Brooklyn on May 24, 1946, with a five-month history of night sweats, chills, fever, and debility. She had cough, hemoptysis, and clubbing of the fingers. Twenty-five years ago she was told she had rheumatic heart disease. For the past one and one-half years she has had dyspnea on exertion.

On admission she presented the typical findings of mitral rheumatic disease with auricular fibrillation. Hepatomegaly was 3 cm. below the costal margin, but the spleen was not palpable. There were petechiae on the abdomen. Blood pressure was 105/80 and temperature was 102° Fahrenheit. Teleroentgenogram was typical of mitral regurgitation. Electrocardiogram revealed auricular fibrillation and myocardial damage. The blood cultures were all sterile. Urine showed occasional red and white blood cells.

Four days after admission the patient almost expired following a left cerebral embolus complicated by shock and myocardial failure. Aside from this, the response to combined penicillin-heparin therapy was uneventful. This was given over thirty-six days and required a total of 97,000,000 Oxford units of penicillin, with 1,300 mg. of heparin. She is now four months post-therapy and is completely free of any bacterial endocarditic activity.

DISCUSSION

The classical symptoms and signs of subacute bacterial endocarditis include chills, fever, diaphoresis, emaciation, splenomegaly, various cardiac symptoms, renal disturbances, tender cutaneous lesions, petechiae, Osler nodes, purpura, pulmonary symptoms, sternal tenderness, cafe-au-lait expression, joint and ocular changes, and central nervous system embolic phenomena. However, the clinical diagnosis of subacute bacterial endocarditis is generally accepted when only the following manifestations are evident: a past history of rheumatic fever with resultant cardiovalvular defect or the presence of congenital heart disease; an insidious onset with lassitude, weakness, anorexia, and low grade fever; cutaneous or visceral embolization; and splenomegaly.

The diagnosis of subacute bacterial endocarditis is authenticated when, in addition to the preceding, the blood culture is repeatedly positive, the infecting

organism being preponderantly the nonhemolytic type of streptococcus. With persistence and proper techniques, positive blood cultures can be obtained in 85 to 95 per cent of cases.

It is evident from a review of the case histories (Table I) that these eleven patients presented the customary protean clinical manifestations which typify this disease. Apart from the sterile blood cultures, all of the requisite diagnostic criteria were fulfilled. All had primary cardiac lesions, nine rheumatic, one congenital, and one atherosclerotic; all had prolonged fever of varying degree, and eight (73 per cent) had embolic phenomena and/or splenomegaly.

The blood cultures were repeatedly sterile in all eleven patients despite assiduous efforts to identify the infecting organism. The designated diagnosis of subacute bacterial endocarditis of undetermined origin, therefore, is justified for the entire series. Two patients who succumbed and were necropsied (Cases 1 and 4) had three and twelve sterile blood cultures, respectively, and yet had typical thromboulcerative endocarditis as shown grossly and histopathologically. Significantly, no bacteria could be recovered from the blood or vegetations of Case 1, although organisms were observed in microscopic sections of the patently active endocarditic lesions. The etiological agent either was not recoverable by the elaborate techinques which were employed or was destroyed by native or circulating antibodies. These patients who came to necropsy and presented the typical pathologic picture of subacute bacterial endocarditis would tend to document the entire series because the same rigid diagnostic criteria were employed in all eleven patients.

One of the patients (Case 4) suffered severe intractable myocardial failure associated with the common type of bundle branch block. He deteriorated rapidly because of the progressive cardiac damage and apparently did not survive long enough to receive the lasting benefits from the combined therapy, although the vegetations at necropsy appeared healed. Case 6 also presented the picture of irremediable heart failure of the type seen occasionally following successful treatment of the bacterial endocarditis and now known to be due to severe mutilation of the valves. The clinical and pathologic aspects of this syndrome have been published.[8]

Case 1 was admitted to the hospital in a greatly emaciated and exhausted condition. He appeared cachectic and presented evidences of advanced myocardial and renal disease and a well-developed avitaminosis. This patient was our only frank treatment failure because it was not possible to give him the prolonged therapy needed in these deteriorated patients. Of the entire group of eleven patients this patient most nearly portrayed the clinical picture of the bacteria-free stage described by Libman and Friedberg.[9] If the mechanism of the bacteria-free stage of subacute bacterial endocarditis is the protracted destruction of bacteria with consequent liberation of noxious bacterial proteins one may still conceivably encounter an occasional patient with this classical syndrome who did not receive the benefits of therapy, either because of failure of diagnosis or the use of subcurative doses of the anti-infective agent. If, on the other hand, the so-called bacteria-free stage is merely an active phase of sub-

TABLE I. CLINICAL FEATURES IN SUBACUTE BACTERIAL ENDOCARDITIS OF UNDETERMINED ETIOLOGY

CASE	SEX	AGE	CARDIAC PRIMARY LESION	DURATION OF ILLNESS (MONTHS)	ONSET WITH UPPER RESPIRATORY INFECTION	FEVER	EMBOLIC PHENOMENA	SPLENOMEGALY	ANEMIA	ARTHRALGIA	STERILE BLOOD CULTURES (NUMBER)
(1) C.M.T.	M	48	Rheumatic	18	Yes	Yes	Yes	Yes	Yes	No	3
(2) A. R.	M	41	Rheumatic	48	Yes	Yes	Yes	Yes	No	Yes	7
(3) S. F.	F	28	Rheumatic	2½	Yes	Yes	No	Yes	Yes	No	15
(4) S.M.F.	M	50	Rheumatic	4	Yes	Yes	No	No	No	Yes	12
(5) J. L.	F	35	Congenital	½	Yes	Yes	Yes	No	Yes	Yes	14
(6) A. S.	M	42	Rheumatic	5	No	Yes	Yes	Yes	Yes	Yes	11
(7) M. S.	M	48	Atherosclerotic	2	Yes	Yes	No	No	No	Yes	7
(8) E. L. S.	F	25	Rheumatic	4	Yes	Yes	Yes	Yes	Yes	No	20
(9) L. G.	F	44	Rheumatic	12	No	No	Yes	Yes	Yes	Yes	18
(10) L. R.	M	20	Rheumatic	1½	Yes	Yes	Yes	No	No	Yes	11
(11) H. W.	F	51	Rheumatic	5	Yes	Yes	Yes	No	Yes	No	5

acute bacterial endocarditis wherein the bacterial agent can not be identified or isolated, fewer of these patients should be encountered as more of them are properly catalogued and given the benefit of curative therapy.

Of the eleven cases, ten (91 per cent) were considered to have been successfully treated, clinically arrested, or cured (Table II). Because of the lack of a recoverable infecting organism, a treatment program predicated on its behavior in the test tube could not be planned. It was necessary, therefore, to conduct the treatment on a trial and error basis by observation of the clinical response. As a result, some of the patients were placed on our minimum standard program of 500,000 Oxford units daily for five weeks with requisite doses of heparin. If they did not respond favorably, that is to say, if the temperature did not fall promptly within a week and the splenomegaly did not begin to recede, or there was a persistence of embolic phenomena, it was obvious that the dosage schedule was inadequate and the treatment was therefore intensified. There was no hesitancy in revising the penicillin dosages upward rapidly to two million units a day, five million units a day, and even, in Case 8, to ten million units a day. Of the eleven patients, four responded successfully to one span of treatment of three to six weeks, requiring an average of 18 million units of penicillin. Case 5 finally responded satisfactorily after her daily penicillin dosage was increased to five million units. She required nine and one-half weeks of treatment totaling 215,000,000 units of penicillin. Case 8 did not respond to prolonged and repeated courses of penicillin therapy. Finally, as a last resort this patient was placed on streptomycin therapy to which she responded spectacularly and is now considered cured. The recovery rate of 91 per cent for this series of eleven patients parallels the expected and anticipated recovery rate in similarly treated cases of subacute bacterial endocarditis infected with nonhemolytic type of streptococcus.

On the basis of the foregoing, in order to terminate the infection under optimum conditions it is imperative to give an adequate span of the therapy as soon as the diagnosis is suspected, even before the results of the blood cultures are known. Ideally, the treatment program in subacute bacterial endocarditis should be based on the identity and test tube behavior of the infecting organism. However, in order to save valuable time, minimize the hazard of serious embolization, and obviate excessive damage to the cardiovalvular apparatus, it is inadvisable to await an unequivocal laboratory confirmation.

A successful outcome in the absence of a positive blood culture serves to confirm an otherwise valid clinical diagnosis of subacute bacterial endocarditis. Very few diseases can be confused with this clinical syndrome which would respond so favorably to this type of therapy. In this connection, the most common diagnostic problem is the differentiation between rheumatic fever and subacute bacterial endocarditis, particularly when they coexist. In actual practice, when confronted with a clinical syndrome wherein the diagnosis rests between subacute bacterial endocarditis and rheumatic fever, a probationary trial of penicillin treatment should be prescribed. The diagnosis resolves itself usually within a week: if the patient has subacute bacterial endocarditis there is appreciable clinical improvement accompanied by recession in temperature; if, however, the patient should have active rheumatic fever, the clinical manifestations re-

TABLE II. TREATMENT PROGRAM AND RESULTS IN SUBACUTE BACTERIAL ENDOCARDITIS OF UNDETERMINED ETIOLOGY

CASE	PREVIOUS TREATMENT	DURATION TREATMENT (WEEKS)	TOTAL PENICILLIN OXFORD UNITS (MILLION)	TOTAL HERAPIN (MG.)	STREPTOMYCIN (GRAMS)	POST-THERAPY OBSERVATIONS (MONTHS)	RESULTS	REMARKS
(1) C. M. T.	Sulfa	3	4.9	1350	None		Failure	Death due to inanition, avitaminosis, cultures of lesions sterile, organisms in microscopic sections of active lesions
(2) A. R.	Typhoid vaccine, sulfa	5	23.7	2100	None	19	Successfully treated	
(3) S. F.	Penicillin	5	22.9	2300	None	19	Successfully treated	
(4) S. M. F.	Penicillin	8	112.0	3100	None		Successfully treated	Died of cardiac decompensation. No organisms in cultures or microscopic sections of healed lesions
(5) J. L.	Sulfa, penicillin	10	215.0	2500	None	13	Successfully treated	
(6) A. S.	None	3	11.0	1100	None	9	Successfully treated	Died 9 months post-therapy of coronary occlusions, left ventricular failure
(7) M. S.	Sulfa	5	17.5	2700	None	8	Successfully treated	
(8) E. L. S.	None	30	250.0	5400	57.5	8	Successfully treated	
(9) L. G.	Penicillin	8	228.0	6100	None	4	Successfully treated	Post-therapy thrombophlebitis cured with subcutaneous heparin Pitkin menstruum
(10) L. R.	Penicillin	6	182.0	2500	6.0	4	Successfully treated	
(11) H. W.	None	5	97.0	1300	4.0	4	Successfully treated	

main static or may, in fact, become aggravated. It has been our experience, as well as that of others,[10,11] that rheumatic fever patients do not fare well in the face of penicillin therapy. We have come to rely on the response to this probationary span of treatment as a differential diagnostic aid.

SUMMARY AND CONCLUSIONS

1. Eleven patients with clinically authentic subacute bacterial endocarditis are reported in whom blood cultures were sterile despite repeated efforts. They represent almost 7 per cent of a total of 166 patients with subacute bacterial endocarditis admitted for treatment with the combination of penicillin and heparin.

2. Of the eleven patients, ten (91 per cent) were successfully treated. Of these ten, nine responded favorably to the conjoint penicillin and heparin therapy. In the tenth patient the infection was finally terminated by streptomycin, after the combination of penicillin and heparin had failed to accomplish this result. Two of the patients who were successfully treated subsequently succumbed to intractable heart failure. One of these patients who came to necropsy presented valves so mutilated as to be incompatible with life. No bacteria could be recovered from the healed valves nor could any organisms be seen in histopathologic sections.

3. One patient who succumbed proved upon necropsy to have had the typical pathologic picture of active subacute bacterial endocarditis. No organism could be recovered from the thromboulcerative endocardial lesions although organisms were observed in histopathologic preparations.

4. As a result of observations in this series of eleven patients, it is apparent that these cases should be treated as promptly and intensively as though they had positive blood cultures. The satisfactory response to treatment serves as a differential diagnostic aid.

We wish to thank Mr. John L. Smith of Chas. Pfizer & Company, Inc., for the generous supplies of penicillin and streptomycin used in the treatment of these patients.

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AURICULAR FIBRILLATION WITH ABERRATION SIMULATING VENTRICULAR PAROXYSMAL TACHYCARDIA

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THE term *aberration* has been defined by Lewis as the "abnormal distribution of a supraventricular impulse in the ventricle." This abnormal distribution of impulses, according to the same author, is due to "defects in conduction through some of the chief Purkinje strands." Lewis[1] illustrates the usually permanent aberration of bundle branch block and the aberration confined to the single ventricular response to a premature beat of supraventricular origin; and he calls attention to aberration in auricular fibrillation, in auricular flutter, and in certain cases of supraventricular tachycardia. One case of the latter type was a child. The auricular rate was about 290 per minute, and occasionally a supraventricular impulse was blocked. On one part of the graphic record, the QRS complex after the pause caused by the blockage was of the usual, narrower form, but the next six complexes were wide. Another beat was dropped; the next QRS complex was narrow; the following complex displayed aberration, but it was not so much deformed as the other wide complexes; and the subsequently appearing complexes were again of the usual, narrower form.

Many other examples of aberration have appeared in the literature, including those seen in supraventricular paroxysmal tachycardia which may simulate ventricular tachycardia. Particularly noteworthy, perhaps, is a patient, described by Barker, Johnston, and Wilson,[2] who had sinus tachycardia and who developed right bundle branch block on two occasions after the administration of quinidine. A very interesting case, similar to ours, was described by Miller.[3] The electrocardiogram of his patient, who had an infarct in the interventricular septum and who died while records were being taken, showed auricular fibrillation. At times the ventricular rate was as high as 185 per minute, without aberration. On other parts of the record, with little change in rate, right bundle branch block was seen. At other times the wide complexes were changed in form, and the author attributed this to ventricular paroxysmal tachycardia. Since the rhythm was unchanged during these paroxysms, we offer the unprovable alternative suggestion that these greatly deformed QRS complexes may be due to a combination of complete right bundle branch block and block in most of the subdivisions of the left bundle branch.[4]

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CASE REPORT

The patient whose electrocardiograms are here presented was a 48-year-old Negro man, whose clinical diagnosis was thyrotoxicosis. He had auricular fibrillation, his blood pressure was 120/80. No clinical evidence of organic heart disease could be found. In this case quinidine was administered in an attempt to stop the fibrillation. The case is presented because it shows periods when the ventricular rate is high, about 200 beats per minute, but with no aberration; and other periods when, with no greater ventricular rate, many successive complexes are of the right bundle branch block type. We believe this case gives information in regard to the mechanism whereby the aberrant complexes, once they appear, are maintained.

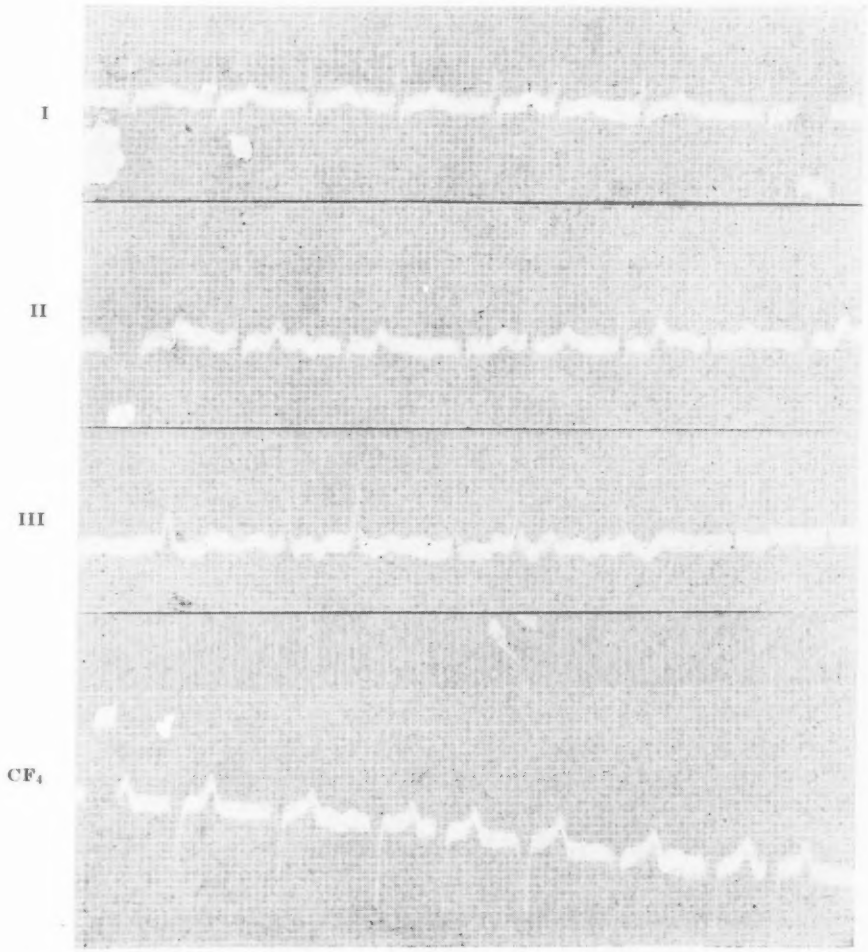

Fig. 1.—Leads I, II, III, and CF_4 taken shortly before the administration of quinidine. Auricular fibrillation with slight aberration shown by the QRS complexes when short ventricular cycles follow relatively long ones.

The Electrocardiographic Findings.—Fig. 1 is the electrocardiogram of this patient taken at 9:25 A.M., shortly before the administration of quinidine. It is a typical example of auricular fibrillation. Two electrocardiograms taken five

and six months previously were similar, except the ventricular rate was not so high. A minimal or slight change is observed to take place in the QRS complexes ending short cycles when these follow long ventricular cycles. Three grains of quinidine sulphate were then administered. Fig. 2 is the electrocardiogram taken at 11:00 A.M., about an hour and a half later. No appreciable change other than a slight slowing has occurred in the auricular complexes. The average ventricular rate is slightly greater. Consistently, throughout this electrocardiogram, when short ventricular cycles follow relatively long cycles, or when very

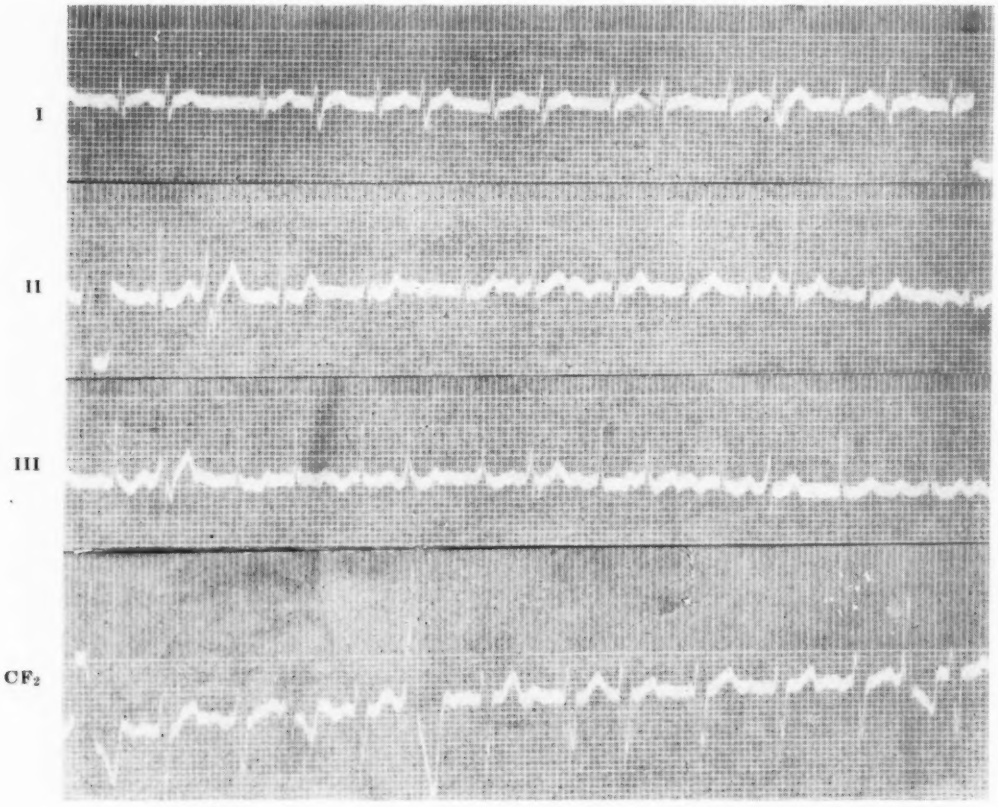

Fig. 2.—Leads I, II, III, and CF_2 taken one and one-half hours after the administration of 3 grains of quinidine sulfate. The auricular fibrillation appears to be a little coarser than before; the ventricular rate is higher. Aberration is now frequent; and when it is present the delay in the right bundle branch varies from slight to probable complete blockage.

short cycles follow cycles of average length, aberration of the QRS complexes is seen. All degrees of aberration are observable. In Lead I, the least change is shown by a slight increase in the amplitude of the R and S waves; but widening of the QRS is not clearly demonstrable. When there is a little more aberration, the S wave widens, the R wave has nearly the height of the usual R wave, and the QRS complex is widened by about 0.01 second. Still more aberration

is shown by further widening of the S wave; and a final stage is seen when the S is very wide and the QRS complex has the typical right bundle branch block form. In Lead III the complex near the middle of the strip is about 0.11 second in duration; while the greatest degree of aberration is shown by a complex near the beginning of the strip, the duration of which is at least 0.12 second. The precordial leads confirm the interpretation of a deficit in right bundle branch conduction for these widened complexes.

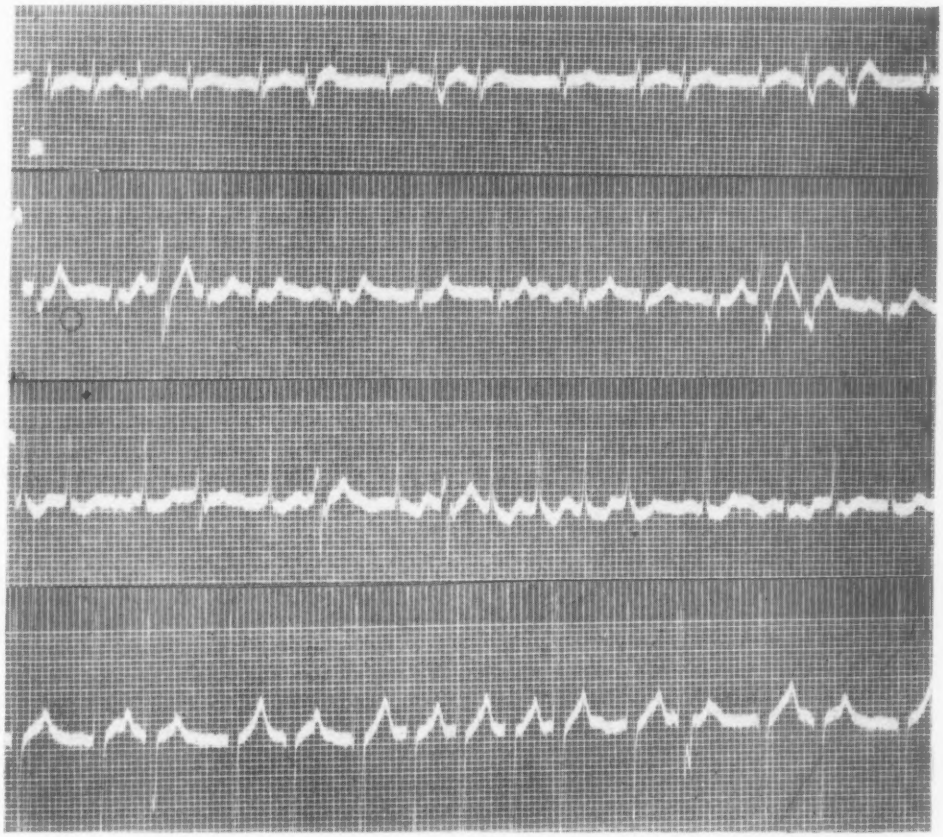

Fig. 3.—Leads I, II, III, and CF_4 taken two hours after Fig. 2.

At 1:00 P.M., the electrocardiogram differs from the earlier one in showing occasional pairs of aberrant complexes (Fig. 3). In only one place on the earlier electrocardiogram did a short cycle follow a markedly aberrant complex. This cycle was 0.31 second, and the QRS complex at its end was not aberrant. In the tracing of which Fig. 3 is a sample, widely aberrant complexes are often followed by short cycles and these are of the following durations, measured in hundredths of a second: 29, 23, 28, 27, 29, 24, and 25. Without exception, the beat terminating these cycles also shows great aberration when the cycle is

0.27 second or less. When the cycle is 0.28 second or longer, the beat ending it shows no aberration.

At 3:00 P.M., nearly two hours after the administration of an additional 6 grains of quinidine sulphate, the rate of the fibrillating auricles has become yet slower and the ventricular rate has increased (Fig. 4). At times, for periods as long as three seconds or more the ventricles are almost, but not quite, regular and the rate ranges from 192 to 196 per minute. In Lead I, a single, markedly aberrant complex is seen. Its width, however, is not over 0.10 second. After 0.29 second, this cycle is followed by a QRS complex which shows no aberration.

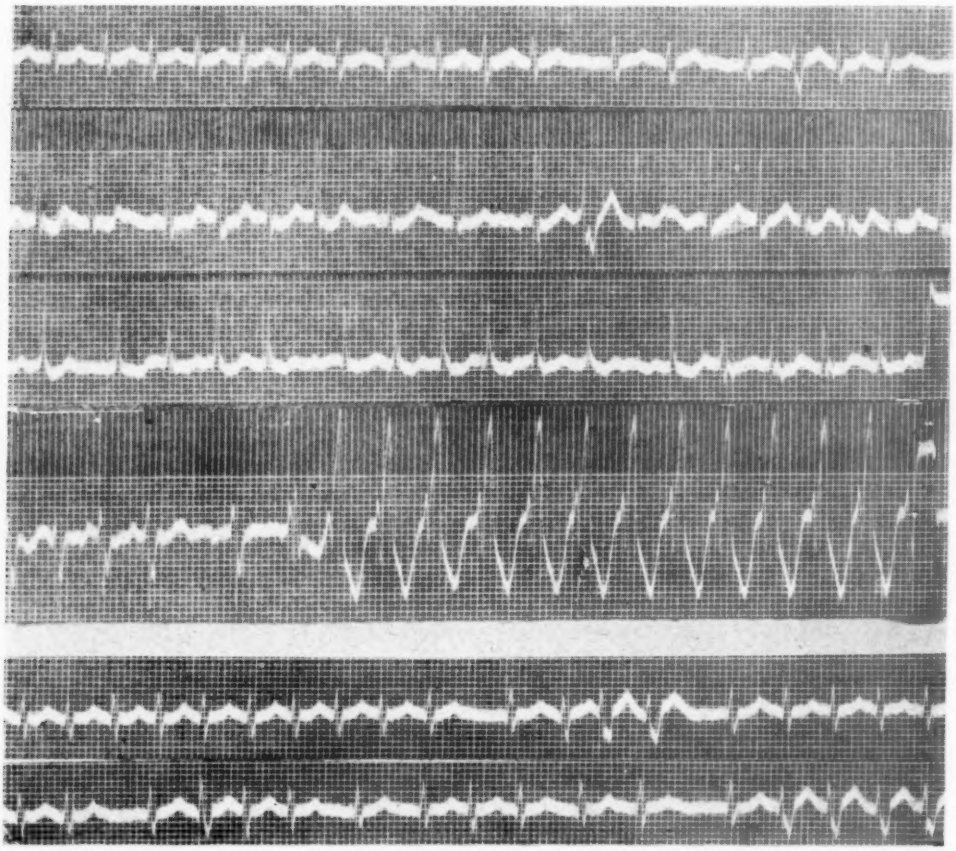

Fig. 4.—From above downward, Leads I, II, III, and CF_I taken after the administration of 6 additional grains of quinidine. The two lower strips are Lead I from a slightly later electrocardiogram. A series of aberrant complexes in Lead CF_I ends just as the standardizing current is sent in. In the last strip a longer series begins, which continued until the film was stopped. Note that the average rate during these series is no higher than the rate on other parts of the tracings, and that the same type of irregularity is present.

In Lead II, the same sequence is seen but the cycle following the wide QRS complex is about 0.33 second. In Lead III, near the end of the strip, a cycle of 0.73 second is followed by a 0.31 second cycle and the QRS complex is 0.12 second in width; the next cycle is 0.32 second, and QRS is wide, as is the next QRS

complex which terminates a 0.34 second cycle. The next cycle is also short (0.34 to 0.35 second), but the QRS complex shows little aberration. In the precordial lead (CF_1), a series of twelve greatly aberrant complexes is seen. The series is ushered in when a very short cycle of 0.24 or 0.25 second follows a cycle of 0.36 second, which is terminated by a moderately aberrant QRS complex. During this period of what looks like ventricular paroxysmal tachycardia, the successive ventricular cycles, measured from the peak of each R wave (not R^1) to the next, are, in hundredths of a second: 30.5, 30.5, 31, 31.5, 30, 30, 31, 29.5, 31, 32, and 32.5; and the next cycle, ended by a narrow complex, is 31.5. Earlier on this same lead there was a period of rapid ventricular action with successive cycles, in hundredths of a second, of 33, 31, 33, 33.5, 30.5, 29.5, 30.5, 29.5, 30.5, 29.5, and 30.5. We here see the same slight irregularity and, toward the end, an even faster mean heart rate. *Yet there is no aberration.* Not counting the series of only three wide complexes, this electrocardiogram and a later one show five other series of wide complexes, and the rate and slight irregularity can always be duplicated on a nearby part of the electrocardiogram which shows no aberration whatever. The series of two or more wide complexes are always ushered in when a short cycle follows a long one or when a very short cycle follows a short one; and, with one exception, they come to an end when there is sudden slight or greater increase in cycle length. In the exceptional instance two wide complexes are separated by an interval of 0.28 second, the next cycle is 0.315 second and the complex is aberrant but not very wide; the following long cycle ends this short series. Another electrocardiogram taken a little later is like this one, except that the rate has gone up to about 200 per minute during the periods of more rapid ventricular action (Fig. 4, lowest strip).

In these electrocardiograms, therefore, we see all degrees of aberration resulting from various amounts of delay in right bundle branch (or "tract") conduction; and we see complexes which suggest complete right bundle branch block. All the complexes in the series of beats which look like ventricular paroxysmal tachycardia are wide and of bundle branch block form. We also see periods of equally rapid rhythm without wide complexes. How are we to account for these findings?

INTERPRETATION

It has been supposed that aberration of a single complex, following an auricular premature beat, occurs when the supraventricular impulse finds one bundle branch or a main strand of Purkinje fibers effectively refractory upon its arrival at the level of the bundle branch.[1] In another paper, it is pointed out that in the normal heart the delay or blocking of the impulse may possibly occur at a higher level,[5] yet the explanation is presumably essentially correct. We have shown that the widening of the QRS complex in our case reached a limit at about 0.12 second and that this suggested complete right bundle branch block. The reason why the blocking persists if the period of rapid rhythm is ushered in by a wide complex, but not if the first complex is narrow, is probably simple. Once an impulse is blocked off from or within the right branch it first enters the left

ventricle. It then passes through the interventricular septum to the right ventricle, and is conducted backward up the right branch to the main bundle where it is blocked, since the main bundle is refractory at this time. We estimate that the time required by the impulse to go through the septum and back up the right branch is at least 0.07 second. If, then, after quinidine, another supraventricular impulse comes down 0.30 second after the one which was conducted aberrantly it reaches the right bundle (or a tract in the main bundle leading into the right bundle) after a rest period in that tissue of not over 0.23 second. This rest is not long enough to allow recovery from refractoriness and to permit the impulse to enter the right branch; therefore, this second impulse is also aberrant. As long as no slightly longer rest occurs *in the junctional tissues*, the right bundle branch block must persist and the electrocardiographic appearance is that of ventricular tachycardia. Once an impulse from above goes through the right branch, even though it is delayed, the cycles may then shorten to 0.28 second or less without aberration.

Aberration occurs when a short cycle follows a long one because the refractory period varies with cycle length. Hence, if a cycle is 0.52 second in this heart after quinidine (Fig. 4, beginning of Lead I, bottom strip), an impulse descending 0.33 second later is delayed but not blocked off from the right ventricle. An impulse following this 0.33 second cycle in 0.285 second experiences minimal aberration. Later in Lead I there is a cycle of 0.77 second. Hence, the refractory period is long, and an impulse descending 0.32 second later is prevented from entering the right ventricle by way of the right branch. It is evident that the *effective* refractory period, which is not necessarily the absolute refractory period but rather a degree of refractoriness which prevents passage of the impulse locally, is longer in the right branch or in some fiber bundle leading to that branch than it is elsewhere. In about 85 per cent of all patients whose electrocardiograms reveal aberration in the distribution through the ventricles of premature supraventricular impulses, it is the right ventricle which is activated late.[5] Obviously, no reason can be given for this fact. It must depend upon some normal structural and/or physiologic peculiarity of the human junctional tissues.

For accuracy it must be noted that the interval between the ventricular beats is not a true measure of the rest interval in the A-V junctional tissues where the blocking occurs.[1,5] It is probably for this reason that minor apparent discrepancies exist between expectation and fact in many cases of auricular fibrillation which reveal aberration of certain QRS complexes. These matters are discussed elsewhere in more detail.[5]

It is not unusual in auricular fibrillation to observe two successive complexes which are widened by aberration, as in this case. It is less common to encounter cases, such as this one, in which ventricular paroxysmal tachycardia is simulated.

SUMMARY AND CONCLUSIONS

The electrocardiogram of a patient with auricular fibrillation is discussed. After the administration of quinidine sulfate the atrial rate was slowed and

the ventricular rate was increased. Numerous aberrant QRS complexes were seen, occurring either singly or in groups of two, three, or more. At several places on the tracings, groups of from six to thirty-three wide, aberrant QRS complexes were seen. At other places, periods of equally rapid ventricular rhythm appeared, but the QRS complexes were narrow. Both when the complexes were wide and when they were narrow, the same slight irregularity in rhythm was found. Reasons are given for believing that the series of wide complexes are due to aberration in the conduction of the supraventricular impulses through the ventricles and that they do not represent ventricular paroxysmal tachycardia, which they closely resemble.

The probable mechanism is described whereby the aberration, once initiated, is maintained.

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THE SUPERNORMAL PHASE OF RECOVERY OF CONDUCTION IN THE HUMAN HEART

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A SUPERNORMAL phase of recovery in excitable tissue was first described in nerve by Adrian and Lucas.[1-3] They found that during a critical period immediately following the passage of an impulse, the tissue was more excitable than usual. An impulse set up during this critical period was conducted faster than the previous impulse, or than an impulse set up earlier or later. Furthermore, a stimulus which would ordinarily be too weak to set up an impulse would be effective if applied during this period. When a region of partial block was present, an impulse which ordinarily would be stopped would pass the region of block if the stimulus were applied during this critical period. To this period of overswing of recovery of excitability and conductivity of the nerve, they applied the term supernormal phase. A similar phenomenon was observed[4] in the turtle heart when the region between the auricles and ventricles was compressed. The phenomenon was more likely to be present when, in addition to compression (injury), there was also marked fatigue.[5] Lewis and Master[6] were unable to demonstrate a supernormal phase in the dog's heart. Hoff and Nahum[7] demonstrated a supernormal phase in the cat's ventricle. However, their experiment showed a supernormal phase of recovery of excitability rather than of conductivity of the ventricular muscle.

In a large number of human cases of partial auriculoventricular block where the requisite injury and fatigue are present, cases are occasionally seen in which a supernormal phase of recovery of conduction seems to be present. There have been a number of reports[8,10-18,21] of isolated cases which supposedly demonstrate this phenomenon. In this report we shall review the literature and differentiate those cases that convincingly show a supernormal phase from those in which some other mechanism appears to be acting. A hitherto unreported case which we consider demonstrates a supernormal phase of recovery will be included as well as a second case of apparent supernormal phase. This second case appears to be more readily explained on an entirely different basis.[11]

ANALYSIS OF THE REPORTED CASES

The first instances of supposed supernormal phase of recovery to be reported in the human heart were described by Lewis and Master[8] in 1924. However,

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both cases were criticized by Wenckebach and Winterberg[9] who explained the mechanism by interference with dissociation rather than a supernormal phase of recovery. Their first case of almost complete auriculoventricular block with sinus impulses being conducted only when the P wave fell in a critical period after the preceding QRS complex seems to be quite well explained by the supernormal phase of recovery. However, an idioventricular rhythm was present, so that dissociation with ventricular capture could also be used to explain the type of conduction seen. Their second case, however, is definitely not an example of the supernormal phase. It is simply a case of partial auriculoventricular block with the Wenckebach phenomenon, with nodal escape beats arising below the region of block so that the sinus impulses appearing immediately after a nodal beat, if not interfered with, were conducted with aberrant conduction.

Ashman and Herrmann's[10] two cases which they believed to illustrate the supernormal phase of recovery can both be explained by other mechanisms. In their first case complete auriculoventricular block supervened whenever auricular slowing occurred, and impulses of sinus origin were again transmitted only when the P wave fell within a critical period (which they considered the supernormal phase) following the idioventricular beat. However, the coincidence of sino-auricular slowing and the intervention of complete auriculoventricular block may be explained by a spontaneous increase in vagus tone producing both effects. The authors did not accept this as an explanation since auricular acceleration did occur later after complete auriculoventricular block and ventricular standstill had been present for some time, yet without resumption of auriculoventricular conduction. However, during ventricular asystole, anoxia of the conducting tissues might conceivably have become so severe that the block was further intensified, in spite of the fact that vagus tone decreased, as indicated by auricular acceleration. Furthermore, with prolongation of cycle length, there is a prolongation of the refractory period of the conduction system.[6] The appearance of idioventricular beats could then result in improved coronary flow and improved conductivity, particularly when associated with a decrease in vagus tone, as was evidenced by shortened P-P intervals. The second case is even less clear than the first and their proof that certain sinus impulses are conducted is not convincing. Both cases contain many idioventricular beats which may give rise to retrograde conduction. The effects of such retrograde conduction (the significance of which will be discussed later) are in no place evaluated; nor are the possible effects of blocked sinus impulses considered. A mechanism similar to the one that Wolferth[11] advanced for his case might well have been operating in both cases.

Wolferth[11] described one case of almost complete auriculoventricular block with occasional ventricular responses to sinus impulses. He did not think the supernormal phase of recovery played any part in this case and he attributed the phenomenon to one of two factors: (1) Prolongation of the rest period in the critical area of block prior to transmission by a mechanism to be discussed in more detail with our second case. (2) Transient improvement of the nutrition in the area of block due to ventricular systole and increased blood flow.

Luten and Pope[12] described a case of 3:1 block with ventricular premature systoles and impulses of sinus origin which were conducted whenever the P wave fell during a certain critical period after the R wave of either a conducted or of an idioventricular beat. They did not think this was due to a supernormal recovery phase of the auriculoventricular conduction system, but thought that it was due to some effect of a previous systole on the ventricular excitability. They excluded the auriculoventricular node because the supernormal recovery phase, or critical period as they call it, had a position in the ventricular cycle which was constant for systoles of the same length, but which, with systoles of different length (as occurred with changes in rate), came at correspondingly different intervals after the beginning of R. However, it is not justifiable to exclude auriculoventricular conduction because of these reasons. It is well known that the refractory period of the auriculoventricular node and common bundle is affected by the preceding cycle length.[6] Furthermore, the interposition of ventricular systole even affects the rate of discharge of the sinus node. This may be seen in some cases of second degree or complete auriculoventricular block where a P-P interval bridging a QRS complex is shorter than a P-P interval which does not include a QRS complex. For these reasons we feel that Luten and Pope's case is an example illustrating the supernormal recovery phase.

Pareja[13] reported a case of partial auriculoventricular block in which he assumed the supernormal phase of recovery to be present. However, because of the shortness of the strip reproduced, it is impossible to be sure that some other mechanism is not acting.

Jervell[14] reported a case of partial auriculoventricular block where the sinus impulses were conducted only when the P wave fell within a certain period following the ventricular complex. This case is doubtful, since in his first record the sudden appearance of complete auriculoventricular block could be a result of sudden increased vagus tone; this variability in vagus tone affecting auriculoventricular conductivity in an irregular fashion could simulate the supernormal phase of recovery. Furthermore, in his second record, the so-called conducted beats could be ventricular premature systoles. However, if a longer record had been presented and the same conditions had held, a supernormal phase would not be ruled out.

Scherf and Schott[15] described two cases of partial auriculoventricular block in each of which auricular impulses occurring in a certain early phase of diastole were conducted faster than those which occurred later in diastole. Their cases resemble our first case, especially since their cases also have no beats of idioventricular or nodal origin, so that retrograde conduction does not complicate the picture. They illustrate the supernormal phase of recovery very well.

Kline, Conn, and Rosenbaum[16] reported two cases which they believed illustrate the supernormal phase of recovery. Their first case resembles the first case of Ashman and Herrmann,[10] and the same objections are pertinent. Their second case was one of complete auriculoventricular block with occasional retrograde P waves following some of the idioventricular beats. They believed that impulses arising in the auricles, although not conducted to the ventricles, produced in the depressed zone a supernormal phase which permitted retrograde

conduction. However, there is no conclusive evidence here for a supernormal phase of recovery, since the retrograde P waves appear whenever the refractory period in the auriculoventricular node produced by partial penetration of the sinus impulse has passed. If it is kept in mind that when the first half of P is being inscribed, or earlier, the sinus impulse has already reached the A-V node, it is apparent that every time a retrograde P does not appear, the sinus impulse is just passing through the auriculoventricular node or has just passed through, so that the retrograde impulse is blocked. This is, in effect, interference with dissociation between the forward conducted impulses of sinus origin and the impulses of idioventricular origin conducted in a retrograde fashion.

Froment, Masson, and Gonin[17] reported two unusual cases of partial auriculoventricular block. Their first case demonstrates the supernormal phase of recovery. Their second case is similar to our second case. Moreover, it showed several instances where retrograde impulses from the idioventricular pacemaker actually reached the auricles and resulted in the inscription of a retrograde P wave. The explanation for the conduction of some of the sinus impulses may be the same as for our second case and for Wolferth's[11] case, and will be further discussed.

Korth[18] presented a case of partial heart block in which impulses coming early in diastole were conducted faster than those coming later in diastole. This, although not described as such by the author, we consider to be due to a supernormal phase of recovery.

The supernormal phase of recovery may possibly account for the path-clearing effect ("Bahnung") of a nodal beat for subsequent auriculoventricular conduction as shown in animal experiments by von Skramlik.[19] A human case supposedly illustrating this phenomenon, in which with periods of complete auriculoventricular block, the first nodal escape of each block period restored the A-V conduction and terminated a Morgagni-Adams-Stokes attack, has been reported by Kisch.[20]

Segers and Van Dooren[21] reported five cases of almost complete auriculoventricular block, four of which showed a slow idioventricular pacemaker with occasional "conducted beats." They believed the conduction occurred whenever a sinus impulse followed an impulse of idioventricular origin within a certain critical period, and called this period the supernormal phase. It would be impossible to rule out the supernormal phase of recovery, but Wolferth's type of explanation might also be used to explain the presence of the occasional conducted beats. However, for either explanation, retrograde conduction would have to be assumed, although no retrograde P waves were present. Furthermore, most of the idioventricular complexes had sinus P waves immediately preceding or immediately following them, and it would be unlikely that the retrograde impulse would reach the critical region of block before the sinus impulse in every case.

Since partial auriculoventricular block is not uncommon, and yet genuine instances of supernormal phase of recovery are seen to be extremely rare, it is not surprising that the supernormal phase of recovery of conductivity could not be found in the mammalian heart experimentally.

CASE REPORTS

CASE 1.—Our first case is that of a 56-year-old white man who was admitted to the Michael Reese Hospital with a myocardial infarct. The patient's course was complicated by acute urinary retention, necessitating a suprapubic cystotomy, and by pneumonitis. The only drugs administered were barbiturates orally, papaverine intramuscularly, and penicillin. No digitalis was given at any time. He was discharged approximately two and one-half months after admission. Early, the electrocardiogram showed the typical changes (Figs. 1 and 4) found in a posteroseptal infarct, with second degree auriculoventricular block. Later, there was some restitution of contour toward the normal, with only first degree auriculoventricular block.

In the electrocardiogram shown in Fig. 1 (Leads I, II, III, CF_2, and CF_4) partial auriculoventricular block is present with what on first inspection might appear to be the Wenckebach phenomenon. However, on closer examination it is seen that the P-R intervals do not gradually lengthen up to the point where the sinus impulse is blocked, and that the P-R intervals bear an unusual relation to the length of the corresponding R-P intervals. In the ordinary case of partial auriculoventricular block with the Wenckebach phenomenon, the P-R interval becomes longer as the R-P interval becomes shorter. Here, however, in many instances the P-R interval becomes shorter in spite of the fact that the corresponding R-P interval also becomes shorter. This is more clearly brought out in Table I, where the R-P intervals are listed in the order of increasing duration. It is seen that they readily fall into four groups. In Group 1, the calculated average R-P is 0.015 second and the average P-R corresponding is 0.575 second. In Group 2, although the average R-P interval is now 0.047 second and is longer

TABLE I. CASE 1. CLASSIFICATION INTO FOUR GROUPS OF THE P-R AND R-P INTERVALS IN THE FIRST FOUR LEADS IN FIG. 1. THE R-P INTERVALS HAVE BEEN LISTED IN THE ORDER OF INCREASING DURATION

GROUP	1		2		3		4	
	R-P (SEC.)	P-R (SEC.)	R-P (SEC.)	P-R (SEC.)	R-P (SEC.)	P-R (SEC.)	R-P (SEC.)	P-R (SEC.)
	0	0.54	0.04	∞	0.12	0.68	0.68	0.50
	0	0.56	0.04	∞	0.12	0.69	0.70	0.48
	0	0.57	0.04	∞	0.12	0.70	0.70	0.48
	0	0.58	0.04	∞	0.13	0.68	0.70	0.48
	0	0.59	0.05	∞	0.13	0.69	0.71	0.48
	0.01	0.56	0.05	∞	0.13	0.69	0.71	0.48
	0.01	0.59	0.05	∞	0.13	0.71	0.71	0.50
	0.03	0.55	0.05	∞	0.14	0.68	0.72	0.48
	0.03	0.56	0.05	∞	0.15	0.66	0.72	0.49
	0.03	0.56	0.06	∞				
	0.03	0.61						
	0.04	0.64						
Average	0.015	0.575	0.047	∞	0.13	0.686	0.706	0.486

than it is in Group 1, the P-R interval is infinity (that is, the sinus impulses are blocked). In Group 3, the average R-P measures 0.13 second and the average P-R interval corresponding to it, 0.686 second. Here, in spite of the fact that

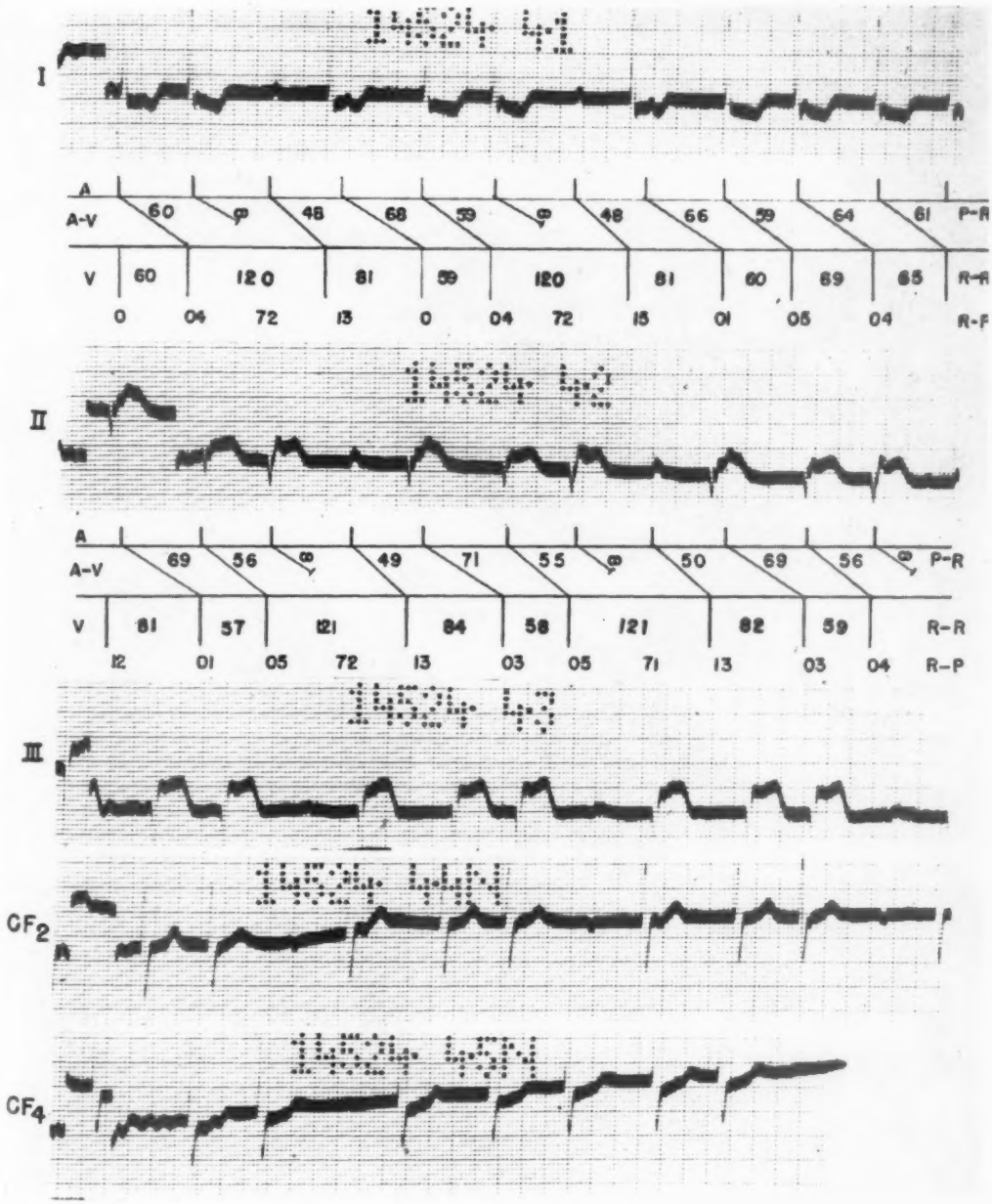

Fig. 1.—Case 1. Limb leads, and Leads CF_2 and CF_4 taken on Oct. 22, 1945. Diagrams demonstrating the conduction of impulses with values in hundredths of a second for the R-P, P-R, and R-R intervals are shown for Leads I and II. Discussed in text.

the average R-P is much longer than in Group 1, the average P-R is also much longer. This is extremely unusual in a case of partial auriculoventricular block. In Group 4 the average R-P measures 0.706 second and the average P-R, 0.486 second. The P-R intervals in this group are the shortest in the series. The most unusual feature is that of Group 1 where, in spite of a short R-P interval, the corresponding P-R is short also, and although not as short as in Group 4, yet

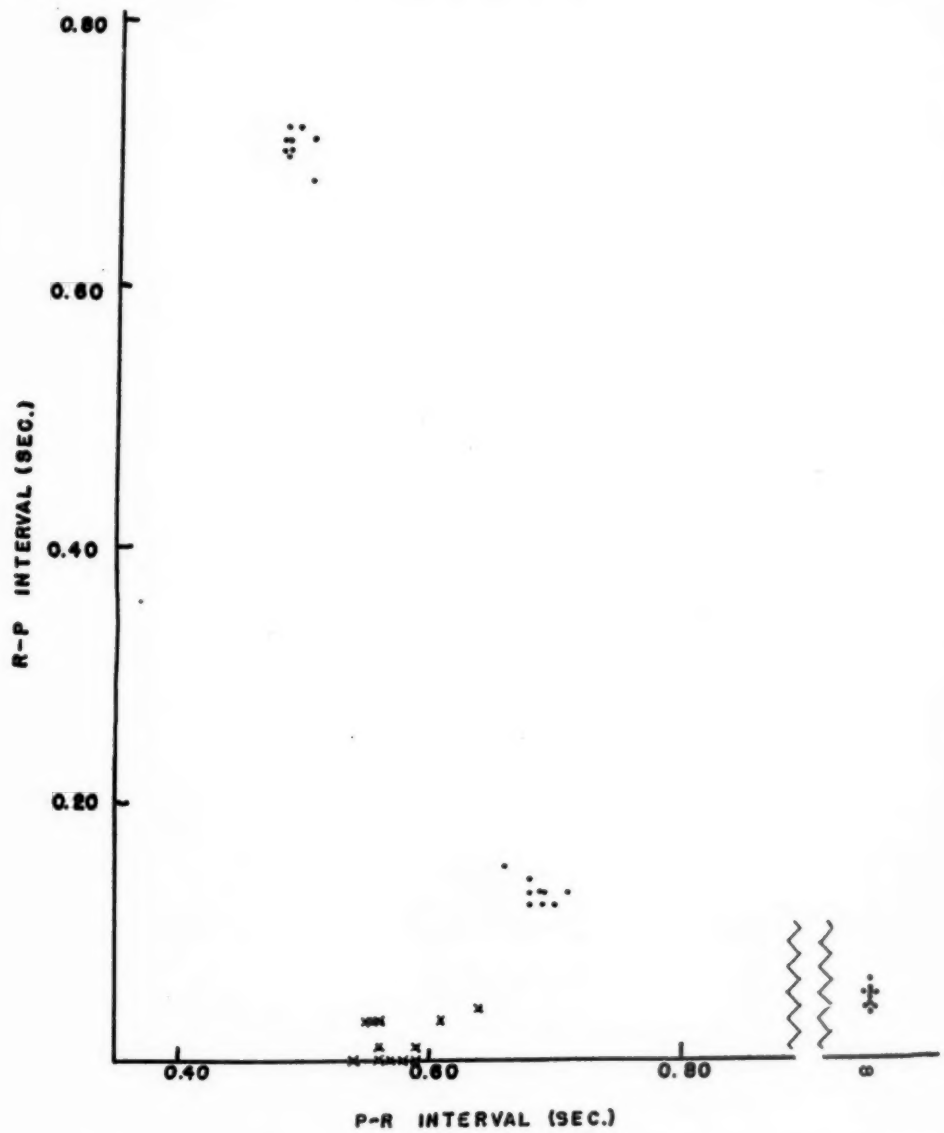

Fig. 2.—Case 1. The P-R and R-P intervals of the record in Fig. 1 are plotted, with the P-R along the abscissa and the R-P along the ordinate. Those beats conducted during the supernormal phase of recovery are indicated by crosses; other beats by dots. Discussed in text.

constantly shorter than in Groups 2 or 3. This phenomenon becomes easily explainable when one realizes that one is dealing with injured conducting tissue where the supernormal phase of recovery may be present. The reason why the sinus impulses are conducted with greater rapidity in Group 1 is that those sinus impulses are the ones that pass through the A-V node or common bundle within

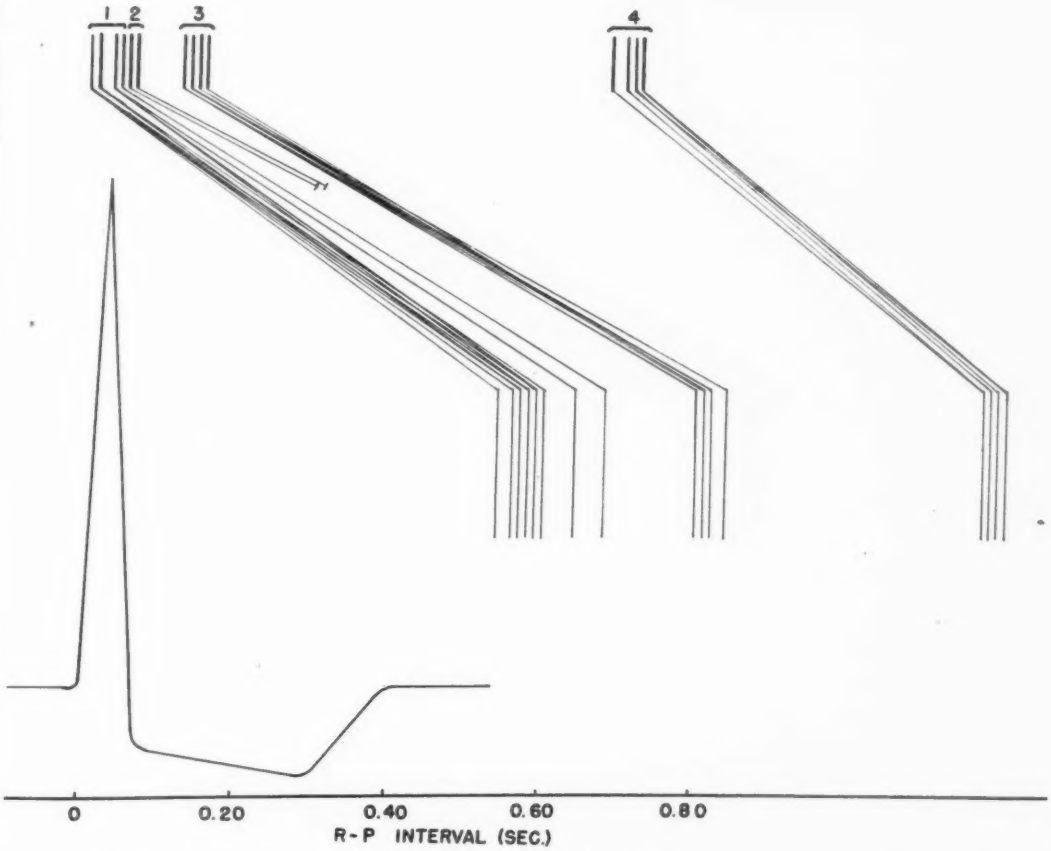

Fig. 3.—Case 1. Diagrammatic representation of the relation of the conducted and nonconducted sinus impulses to the preceding QRS complex. A division into four groups is indicated. In Group 1, the calculated average R-P is 0.015 second and the average corresponding P-R is 0.575 second; in Group 2, the average R-P is 0.047 second and P-R is infinity (blocked); in Group 3, the average R-P is 0.13 second and the average P-R is 0.686 second; in Group 4, the average R-P is 0.706 and the average P-R is 0.486 second. Where values for several beats are identical, the beats are indicated by a single line. This graph is to be compared with Table I.

a critical period of time when the conducting tissue is in the supernormal phase of recovery. The impulses in Group 2 fall just after the supernormal period and are not conducted. Impulses falling as late as those in Group 3 are conducted, but at a rate slower than those that fell within the supernormal period. Those in Group 4 are sinus impulses that follow a blocked sinus impulse, and because of the very long rest period that precedes them, are conducted faster even than

those that fell in the supernormal phase. Therefore, it should be noted that the term "supernormal" refers to the rate of recovery of conduction and not to absolute values of conduction speed. In this case the conduction during the supernormal phase is faster than expected, but not faster than normal. In the cases reported by Scherf and Schott[15] the conduction during the supernormal phase was actually faster than that occurring after a long rest period, namely, after a blocked beat.

The relationship between R-P and P-R and the presence of the supernormal phase is shown in another way in Fig. 2. Here the duration of the R-P intervals is plotted along the ordinate and the P-R along the abscissa. It is seen that the beats exhibiting a supernormal phase (x) fall in a group by themselves, and are outside of the recovery curve connecting the other beats. This is again shown in Fig. 3, the type of diagram utilized by Lewis and Master;[8] the relation of the P waves to the preceding and succeeding QRS complexes is shown.

Fig. 4 shows an electrocardiogram taken two days *before* the one shown in Fig. 1. The same phenomenon may be seen. However, while the paradoxical shortening of the P-R intervals is seen in following any one series up to the dropping of a beat, when the entire group of P-R and R-P intervals are plotted on a graph (Fig. 5) the group of beats (x) which were conducted during the supernormal phase do not fall into as distinct a group as those in Fig. 2. However, for any given R-P, the beat with the shortest P-R is always the one that was considered to fall into the supernormal period. This variation of actual location in the cardiac cycle of the supernormal phase is probably only apparent and is due to fluctuations in auriculoventricular conductivity which displace the supernormal period in the cardiac cycle. These fluctuations in auriculoventricular conductivity will also explain the apparent difference in position of the supernormal phase in the cycle in the records taken two days apart.

Hoff and Nahum[22] believe that in the cat heart and the human heart the supernormal phase, when it occurs, falls on the same portion of the cycle as the U wave. However, as mentioned already, they were recording the supernormal phase of recovery of excitability of the ventricular musculature, and not of the conduction system. Furthermore, since a region of block is present, the apparent position of the supernormal phase in the cycle as derived from the R-P distance of the conducted beat will be determined by two factors: (1) Its actual position; and (2) the degree of conduction delay which will influence the specific time at which the impulse reaches the region where the supernormal phase becomes manifest.

There is an additional factor that affects auriculoventricular conductivity in cases of partial auriculoventricular block where there are variations in cycle length (for example, variations in ventricular rate). This is a phenomenon described by Lewis and Master[6] when they found in the dog's heart that there was a definite change in the recovery curve of auriculoventricular conductivity with varying heart rates. At the higher ventricular rate (shorter cycle length) the recovery curve began earlier, so that a P-R interval corresponding to a R-P interval of given length was shorter for high rates than for low rates of beating;

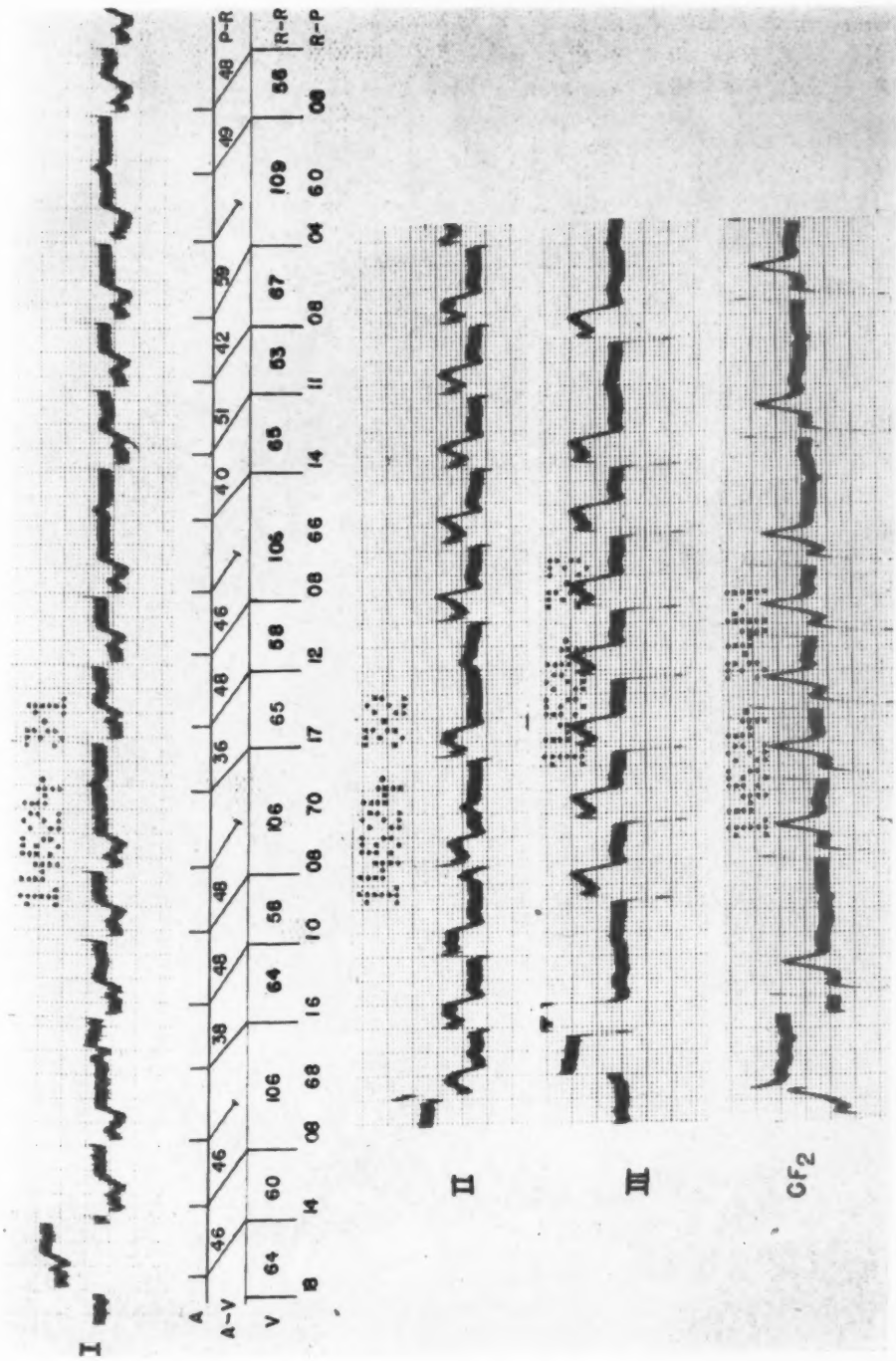

Fig. 4.—Case 1. Limb leads and Lead CF_2 taken Oct. 20, 1945. A diagram demonstrating the conduction of impulses with values in hundredths of a second for the R-P, P-R, and R-R intervals is shown for Lead I. Discussed in text.

this was found over the greater part of the recovery phase up to the time the curves crossed or ran together into a common plateau. Furthermore, they found that in passing from a slow to a faster rate of response it is the rule for the recovery curve to change after a single beat of the faster rhythm, so that the type

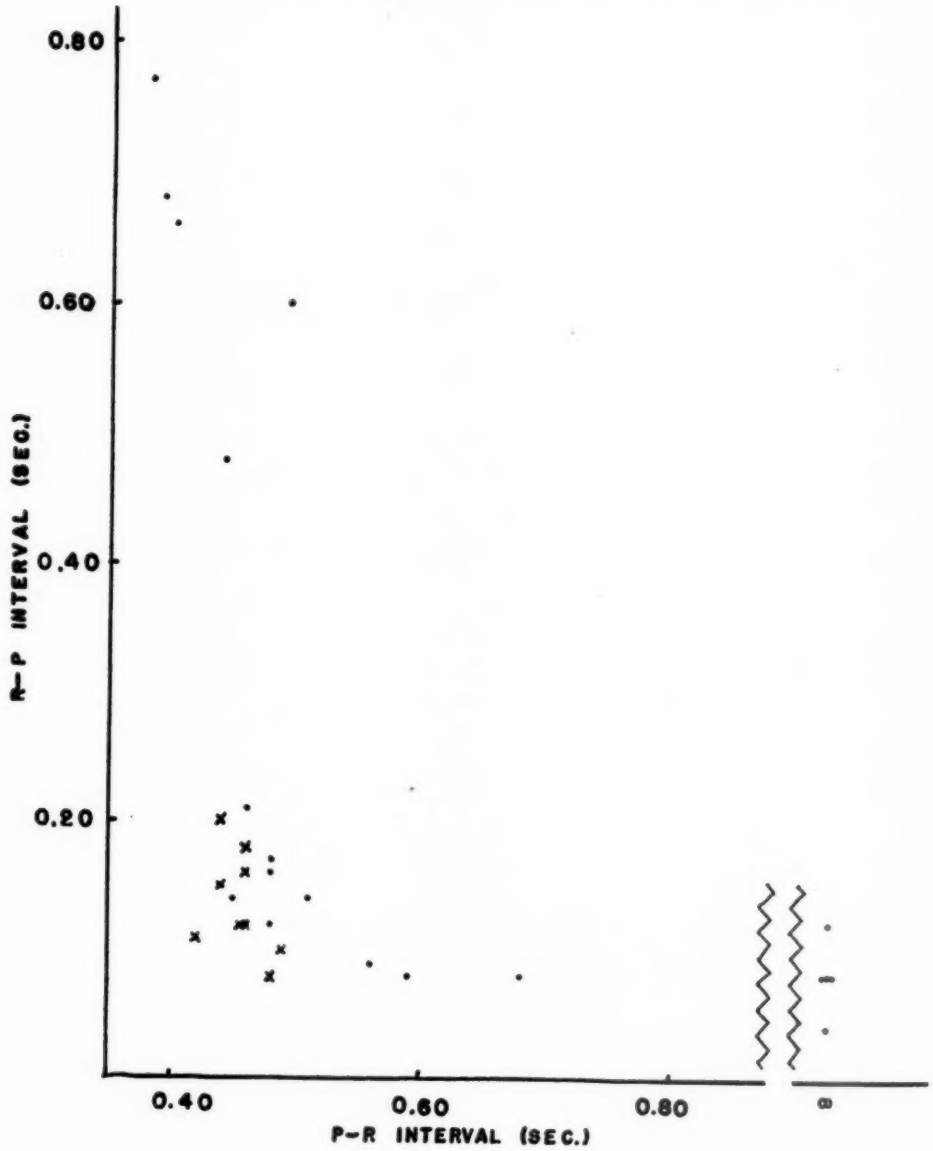

Fig. 5.—Case 1. The P-R and R-P intervals of the first two leads in the record in Fig. 4 are plotted with the P-R along the abscissa and the R-P along the ordinate. Those beats conducted during the supernormal phase of recovery are indicated by crosses; other beats by dots. For any given R-P the beat with the shortest P-R is the one that was observed in the record to fall in the supernormal phase of recovery. Discussed in text.

of recovery curve depends primarily on the length of the cycle which immediately precedes it. This may be restated: the refractory period of the conduction system will shorten when the cycle length shortens (rate increases). It is important to realize that the refractory period and recovery curves described by Lewis and Master are actually those of the tissues in which the variations of conduction are occurring and not of the excitability of the ventricular musculature.

This principle may be applied to a certain extent to our Case 1. Here it may be seen that the paradoxical shortening of the P-R intervals does often occur whenever the cycle length (R-R interval) shortens preceding the conducted beat. Since the R-R following a blocked beat is shorter than the R-R including the blocked beat, it is usually the second sinus impulse following one which is blocked that is conducted faster than expected. Thus, this mechanism may be acting in addition to the supernormal phase in our case. It is unlikely, however, that it alone is the factor responsible for the paradoxical shortening of the P-R intervals, *since there are several instances in the series where a shorter P-R interval appears even when the preceding cycle length is longer.* This may be seen usually where there are more than three consecutive conducted beats, as, for example, in the last group of P-R intervals in Leads I and CF_4 of Fig. 1, where the paradoxical shortening of P-R is still present even though the preceding cycle has become longer than the one preceding it. Moreover, it is doubtful that the effect of relatively slight variations in preceding cycle length on the refractory period of the conduction system would be so marked as to overcome the effect of marked shortening of the rest periods (R-P intervals) and give such a bizarre finding. In typical partial auriculoventricular block with the Wenckebach phenomenon, the P-R intervals, while becoming prolonged, it is true, to a *decreasing* extent before one is blocked, never actually get shorter than the preceding one. It is interesting to note that although Lewis and Master explained this feature of the Wenckebach phenomenon on the basis of changing recovery rates due to changes in cycle length, Decherd and Ruskin[23] have shown that it could be explained merely by the type of recovery curve present, the conduction time after complete recovery, and the auricular rate, without assuming a changing absolute or relative refractory period.

Our first case is thus seen to illustrate quite well the supernormal phase of recovery. Especially important is the absence of beats arising in nodal or ventricular pacemakers, so that the possibility of retrograde conduction does not complicate the picture.

CASE 2.—Our second case is that of a 65-year-old white woman with arteriosclerotic heart disease who was admitted to the hospital because of Morgagni-Adams-Stokes attacks.

An electrocardiogram (Fig. 6) revealed the presence of almost complete ariculoventricular block with occasional conducted beats. Comparison of the length of R-P intervals of the conducted beats with that of the blocked beats shows that we are not dealing with a case of dissociation with interference in the presence of a second degree auriculoventricular block. It was found that those

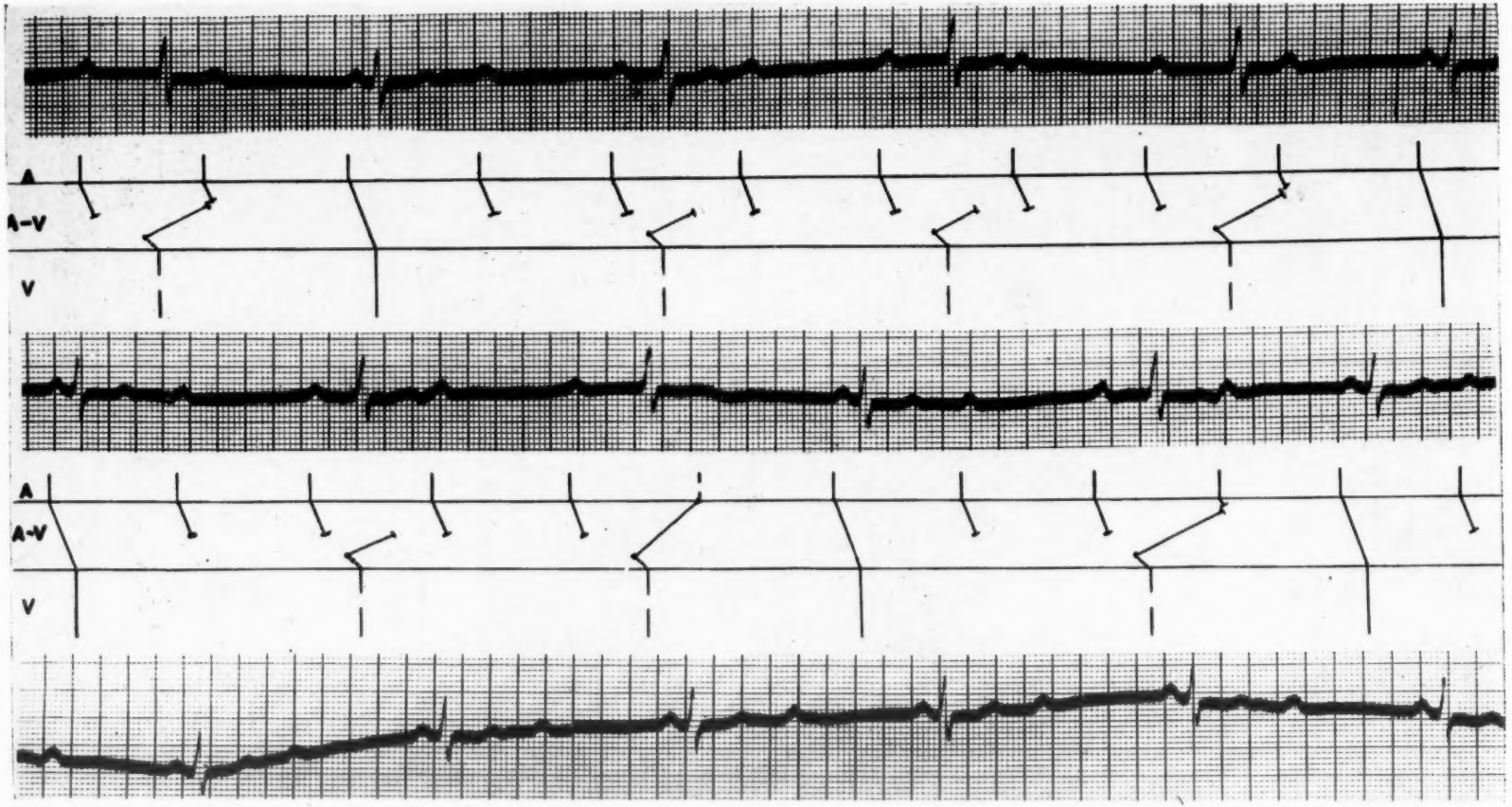

Fig. 6.—Case 2. Three strips, all of Lead II, are shown. The top two strips are continuous, part of the top strip being reproduced again in the middle strip. The mechanism of conduction and interference is shown diagrammatically for these strips. A fusion P wave (indicated by broken line) is fused with the third T wave in the middle strip. The bottom strip taken several minutes after the top two strips shows 2:1 conduction with a faster sinus rate. Nodal beats are indicated by a broken line. Discussed in test.

sinus impulses that were conducted always bore a definite relationship to the preceding QRS complex. One might then attempt to explain the conduction of some beats on the assumption that they fell during the supernormal phase of recovery of the greatly depressed auriculoventricular node or common bundle produced by a retrograde impulse of the nodal beat. This is the type of explanation utilized for several similar cases[10,16] in the literature. Yet, if the conducted impulse were falling into a supernormal phase, the supernormal phase in this case would fall an unusually long time after the QRS complex, longer than in any case yet reported, and, moreover, after a blocked sinus impulse.

The P wave just preceding each conducted P wave bears a certain relationship to the nearest preceding nodal beat. It may be postulated that in the cases where the sinus impulses are blocked, these impulses are conducted to a certain region of the A-V junction where the block is especially marked, and it is in this region that the complete blocking occurs. Furthermore, each succeeding impulse penetrates to a certain extent into this region but usually does not get through. If, however, a nodal beat occurs with retrograde conduction, the retrograde impulse may reach the region of block sooner, traverse it, and interfere with (block) the sinus impulse above this region of severe block. Then, when the next sinus impulse reaches this region of severe block, this region having rested for a longer period of time than before, will now permit the sinus impulse to pass through. If, however, the nodal beat comes too soon after a sinus impulse has penetrated the region of marked block, then retrograde conduction from the nodal pacemaker would not penetrate up and interfere with the next oncoming sinus impulse. This explanation is that given by Wolferth[11] in his case. The mechanism is indicated by the diagrams in Fig. 6.

It will be noted that the third T wave in the second strip in Fig. 6, although produced by a fusion of P and T, is of much lower amplitude than would be expected from a fusion of a sinus P wave and an upright T wave of an amplitude seen elsewhere in the record. For this reason, it is quite probable that the P wave there recorded is not a sinus P wave, but is a retrograde P wave (inverted), or more likely yet, a fusion P wave (a P wave which is inscribed while the auricle is being invaded by an impulse from the sinus node and from below by a retrograde impulse from the A-V node). In the explanatory diagram shown just below this strip in the same figure, this P wave is represented as a broken line, and the line indicating retrograde conduction through the A-V node is shown entering the auricle. The slope of this line is represented as being steeper because the preceding P-R distance (R of the nodal beat) is long. Because the rate of retrograde conduction usually depends on the time elapsing between the discharge of the sinus node (even when the impulse only penetrates into the A-V node without reaching the ventricles) and the subsequent discharge of the A-V pacemaker, the duration of the R-P (retrograde) interval may be assumed to vary in an inverse fashion with the duration of the P (sinus)-R interval.

This mechanism was readily applied to a long record. During the course of taking this record, for a varying period of time, this patient developed relatively persistent 2:1 auriculoventricular block. This is seen in the bottom strip in Fig. 6. However, it is noted that the P-P distance in the bottom strip is shorter than

in the two upper strips. This speeding up of the sinoauricular pacemaker was probably associated with a decrease in vagus tone (or increase in sympathetic tone) which would also result in improved conductivity in the auriculoventricular node and common bundle.

While in Wolferth's case[11] there was no direct evidence of retrograde conduction, there is such evidence present in our case. However, even more clear-cut proof of retrograde conduction was found in the second of two cases reported by Froment, Masson, and Gonin.[17] Their case could be considered to illustrate a supernormal phase of recovery. We believe, however, that the explanation of interference within or below the auricles between forward conduction of a preceding sinus impulse and retrograde conduction of a nodal impulse, which then facilitates the conduction of the next sinus impulse, is an alternative one. The presence of retrograde P waves tends to substantiate this explanation.

SUMMARY

1. An analysis of the reported cases of supernormal phase of recovery in the human heart is presented. In only five of these cases could the supernormal phase of recovery be considered present; in the others, different mechanisms appeared more likely.

2. A new case of partial auriculoventricular block is presented which demonstrates the supernormal phase of recovery. It was shown that the effect of cycle length on the refractory period was not sufficient to explain the paradoxical type of conduction exhibited and that a supernormal phase of recovery of the conducting tissue was responsible.

3. A second case of partial auriculoventricular block is presented which on first examination would seem to exhibit a supernormal phase of recovery. However, it was shown that auriculoventricular conduction occurred whenever a retrograde impulse reached the critical area of block prematurely, thus prolonging the succeeding rest period, and hence facilitating conduction of the next sinus impulse. This mechanism, reported by others, could be applied to some of the cases in the literature.

ADDENDUM

Since submitting our report, Segers and Denolin* reported a case of a 25-year-old man without evidence of heart disease, with marked sinus arrhythmia, and no A-B block, in which slowing of the sinus rate was associated with slight lengthening of the P-R intervals (0.20); speeding up of the sinus rate was associated with shortening of the P-R intervals (0.14). They attributed this to the supernormal phase of recovery. They did not believe that the findings could be due to changes in vagosympathetic tone because of the marked irregularity of the arrhythmia. However, this argument is not convincing because of the coincidence of the shorter P-R intervals with a faster sinus rate, making it quite likely that variations in vagosympathetic tone were responsible for the variations in A-V conduction. The possibility of a wandering pacemaker, as evidenced by changes in P-wave contour, could also be responsible for variations in duration of the P-R intervals. Another unusual characteristic of their case is the location of the supernormal phase of recovery in the cycle, and its long duration (0.40 to 0.70 second after the R wave).

*Segers, M., and Denolin, H.: Etude de la Transmission Auriculo-Ventriculaire III. La Phase Supernormale de la Conduction, Acta Cardiologica **1**:279, 1946.

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THE ELECTROCARDIOGRAM IN NEUROCIRCULATORY ASTHENIA, ANXIETY NEUROSIS, OR EFFORT SYNDROME

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SOME uncertainty has existed concerning the normality of the electrocardiogram in neurocirculatory asthenia because of occasional reports of unusual findings mingled with the general failure to discover any specific electrocardiographic pattern.

Lewis[10] during the first World War found essentially normal electrocardiograms in cases of effort syndrome or neurocirculatory asthenia without characteristic pattern. In 1934 Craig and White[3] reported an analysis of the electrocardiograms of thirty-five cases of "pure neurocirculatory asthenia"; in fifteen there was sinoauricular tachycardia (rate 110 to 160 per minute), in eight the T waves were diphasic in Lead II and inverted in Lead III, in six there was slight left axis deviation dependent on obesity, in five slight right axis deviation, and in one bigeminy due to auricular premature beats cleared by exercise. The next year (1935) Graybiel and White[4] reported the discovery of inverted T waves in Leads II and III in seven cases (three men, four women) of neurocirculatory asthenia with no evidence of heart disease. Later, White and associates[12] concluded that such findings were dependent in major part on a vertical position of the heart and were generally corrected by a change to a supine body position, although in some cases sympathetic overstimulation, as by alarm or by the actual injection of adrenalin, could also markedly lower or even invert the T waves in Lead II, findings concurred in by other investigators. These changes can be produced whether or not there is neurocirculatory asthenia, though some cases with neurocirculatory asthenia do possess a slender body build and are easily affected by fright. Battro and Cobo[1] found slight elevation of S-T segments in some cases of neurocirculatory asthenia but this is a common finding in normal subjects. Hyperventilation has been stated by Thompson[11] and by others to depress the S-T segment and to lower or even invert the T waves in any or in all leads. Master[9] and others have reported the frequent occurrence of right axis deviation in neurocirculatory asthenia apparently related to body

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build, but Master confined his observations to the "slender or asthenic type of individual with a low disphragm and small heart." Finally, prolongation of the P-R interval has been noted in some few cases, as by Logue, Hanson, and Knight.[8]

A detailed study of soldiers with neurocirculatory asthenia by Cohen, Cobb, White and their colleagues[2] during World War II presented the opportunity to analyze their electrocardiograms in detail. The present paper summarizes the data secured in the analysis of the tracings of fifty male soldiers with neurocirculatory asthenia and fifty civilians, men and women, diagnosed as having anxiety neurosis and neurocirculatory asthenia in the psychiatric and medical clinics of a civilian hospital, a total of 100 young persons with this condition.

FINDINGS

Rhythm.—Normal rhythm was found in all cases, with a moderate amount of sinus arrhythmia in eleven.

Rate.—In the majority of cases (fifty-one) the heart rate was in the range of 70 up to 90; seven had rates below 70; twenty-two, from 90 to 100; and twenty, 100 or more beats per minute. This range of rate is somewhat higher than that customarily found in normal young adults unaccustomed to electrocardiography; for example, in the series of 1,000 healthy young aviators studied by Graybiel and his associates[6] the range of heart rate was from 38 to 110, with the mean at 63.8, and over 100 beats per minute in only three cases.

P Wave.—The auricular complexes were within normal limits in all cases, although very small in three and diphasic in Lead III in one case.

P-R Interval.—The P-R interval measured 0.12 to 0.18 second in eighty-six cases, 0.11 second in one, 0.18 to 0.20 second, inclusive, in eleven, and over 0.20 second in two cases (0.22 and 0.24, respectively). It is probable that some chronic abnormality of auriculoventricular conduction existed in these two cases although there was no other evidence of heart disease. Nor was there any sign of active rheumatism.

QRS Wave.—The QRS complexes were within normal limits in shape, amplitude, and duration in all cases. Small Q deflections were found in Lead I in three patients and in Lead II in nine. Moderate Q deflections were present in Lead II in one case and in Lead III in ten. The duration of the QRS waves measured less than 0.10 second in eighty-six and just 0.10 second in fourteen. None showed intraventricular block.

Electrical Axis.—Measured according to Einthoven's triangle, the angle of the electrical axis ranged from 0° up to 90° in eighty-six cases, being 45° or more in sixty-three of these. In eleven subjects the angle was 90° or over, and it was less than 0° in only four. In only one case was the angle more minus than −30°. Thus, in nearly three-fourths of all the cases the angle was nearer the vertical than the horizontal.

Q-T Duration.—The duration of systole as measured by the time from the beginning of the QRS wave to the end of the T wave equalled 0.30 to 0.35 second inclusive in seventy-eight cases, a perfectly normal duration for the heart rate which ranged mostly from 70 to 90 per minute, or a bit more or less. The duration was more than 0.35 second in twelve cases with the slowest pulse rates (50 to 55 in four cases and 60 to 70 per minute in six others); in no case was the measurement over 0.40 second. In seven patients the Q-T time was below 0.30 second but in none below 0.25 second; the shorter systoles were found, as was to be expected, in persons with faster heart rates, 100 or more per minute in all, with the fastest rate, 115 per minute, in the case with the shortest systole (0.25 second).

S-T Segment.—The S-T segments were flat in the limb leads in sixty-seven cases, slightly elevated in twenty-six (not over 0.5 mm. in Lead I or over 1 mm. in Leads II and III), moderately elevated in three (1.5 mm. in Lead III in one, 2.0 mm. in Lead III in one, and 2.0 mm. in Leads II and III in one), and slightly depressed in four cases (0.5 mm. or less in Lead II and in one case 1 mm. in Lead III). In Lead IV it was common, as it is normally, to find an elevation of 1 mm.; in one case there was an elevation of 2 mm. and in one other of 2.5 mm.; in no case where Lead IV was taken was its S-T segment depressed.

T Wave.—The T waves were upright in Lead I in every case, averaging 1.5 to 2.0 mm.; in seven cases the T waves were only 0.5 mm. high (or less) in this lead. In Lead II the T waves were upright in all cases except three, being flat in two of these and inverted (−1.5 mm.) in one; in these three exceptions the heart tended toward the vertical in position (axis angle 60° to 90°) and the first two may have their explanation therein, but the third with clearly negative T waves showed also negative T waves in precordial Leads CF_2, CF_4, CF_5, and CF_6 (−3.5 mm. in CF_4 and −3.0 mm. in CF_5) which strongly suggests some type of coincidental myocardial or pericardial involvement in that 20-year-old soldier. In Lead III the T waves were upright in thirty-eight cases, level in thirty-six more, diphasic in two, and inverted in twenty-four. Of the sixty cases in which Lead IV was recorded, fifty-seven showed upright T waves, two slight late notching, and one, referred to previously, distinct inversion not only of T_4 but of the T waves in the precordial leads from Positions 3 to 6, inclusive.

Precordial Leads.—A routine Lead IV was taken in sixty of the 100 cases and was clearly normal in fifty-seven. The QRS waves were an average normal in all sixty cases. In two cases the T waves were flat with slight late notching, the cause of which was not evident; there was no indication of heart disease; both had axis angles of 60°. The one case with clearly abnormal T waves in multiple precordial leads has been referred to previously.

Special Studies.—The effect of body position and of respiration was tested in six cases, little change in the electrocardiogram resulting except for slight axis deviation associated with change in heart position similar to changes described during respiration in healthy subjects. Strenuous exercise gave tachy-

cardia and lower T waves in the two cases so tested. Twelve cases subjected to the Master two-step test showed no changes in the electrocardiogram save for an increase in heart rate. In three cases hyperventilation led to an increase in heart rate in all three, no change in T waves in one, slight elevation of T_2 in one, and slight lowering of T_1 and T_3 in the other. The alarm reaction (by revolver shot), tested in Lead II, caused an increase in heart rate in four cases, no change in T waves in two cases, slight lowering of T waves in one case, and inversion of T_2 in the fourth case, similar to findings in healthy subjects.

DISCUSSION

A review of the literature, our own clinical experience during the past twenty-five years, and the present detailed analysis of 100 cases indicate the nonexistence of any characteristic pattern or pathognomonic evidence of neurocirculatory asthenia in the electrocardiogram. The variations from the average normal resting tracing can and should be attributed to unusual position of the heart (as a rule, extreme verticality), to the effect of exercise, excitement (alarm, for example), possibly overventilation, and, in very rare cases, quite probably to otherwise nonevident slight pathologic conditions. From these data it seems unlikely that simple emotion alone, such as "anxiety," leads to electrocardiographic changes as suggested by Loftus, Gold, and Diethelm.[7] All 100 of our cases were examples of clinically diagnosable anxiety neurosis, and yet their electrocardiograms differed in no obvious way from those of healthy individuals. Prolongation of the P-R interval which has been noted in a few cases of neurocirculatory asthenia is to be ascribed to either an extreme normal variation or to coincidental heart disease, probably rheumatic (acute or chronic), not otherwise manifested, and is not to be attributed to the neurocirculatory asthenia itself. Thus, our two cases with prolonged P-R intervals very likely had suffered at some time in the past from some process that had slightly scarred their auriculoventricular conduction tracts, and our one case with persistently abnormal T waves in Leads II and III and precordial Leads CF_3 to CF_6 inclusive very probably had some unrecognizable type of myocardial or pericardial involvement. All 100 cases were carefully selected as characteristic instances of neurocirculatory asthenia in youth without clinical evidence of heart disease.

Had we found an appreciable number of clearly abnormal electrocardiograms in this series, would we have attributed the abnormalities to this condition itself? In all probability we would have done so unless the cases themselves had shown other definite causes for the abnormality. The very few unusual findings in this group were comparable both in type and extent to those which have been reported in the study of 1,000 healthy subjects.[6]

SUMMARY AND CONCLUSION

An analysis of the electrocardiograms of 100 cases of neurocirculatory asthenia, half soldiers and half civilians, has revealed no characteristic pattern. The few variations from the average normal record are those usually encountered in a group of healthy young men, and either are associated with well-known

factors such as body build, pulse rate, and posture, or are the effect of past illness.

One may, therefore, conclude that the electrocardiogram is normal in neurocirculatory asthenia.

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THE RELATIONS OF T_1 AND T_3

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SEVERAL investigators[1-3] have recently pointed out that an upward T_1 which is less than T_3 in amplitude ($T_1 < T_3$) is frequently a sign of myocardial infarction. No adequate explanation for this interesting observation has appeared; furthermore, T_1 may be less than T_3 in a normal person.[1-3] However, when persons who show a $T_1 < T_3$ pattern are studied by means of unipolar leads, the explanation for this phenomenon becomes evident.

MATERIAL AND METHOD

The tracings of 500 patients were reviewed for this study. In all these cases, unipolar extremity leads and multiple unipolar precordial leads were taken in addition to the three standard leads. The unipolar extremity leads were taken with the author's method of obtaining "augmented" unipolar extremity leads.[4] All the unipolar leads were taken with the author's modification of Wilson's indifferent electrode of zero potential.[4] Unipolar extremity leads were taken from the left arm, the right arm, and left leg. Precordial leads were taken over the following points on the chest wall: V_1, precordial electrode over fourth intercostal space to the right of the sternum; V_2, over the fourth intercostal space just to the left of the sternum; V_3, between V_2 and V_4; V_4, over the fifth intercostal space on the left midclavicular line; V_5, on the left anterior axillary line at the level of V_4; and V_6, on the left midaxillary line at the level of V_4.

In this series, twenty-five tracings showed a $T_1 < T_3$ pattern. Seventeen were from persons with normal hearts, or with right or left ventricular hypertrophy. Eight patients had anterior infarction.

RESULTS

General Remarks.—Leads I and III are related, regardless of what their actual patterns are because the potentials of the left arm take part in the formation of both these leads. Lead I equals left arm minus right arm, and Lead III equals left leg minus left arm. As a matter of fact, the relations between the patterns of the left arm lead and Leads I and III can be expressed mathematically as follows:

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$$\text{left arm} = \frac{I - III}{3}.$$[5]

The proof of this is as follows:[5]

The above equation can be rewritten,

$$\text{left arm} = \frac{(LA - RA) - (LL - LA)}{3}$$

$$= \frac{LA - RA - LL + LA}{3}.$$

Since $RA + LA + LL = O$,[4,5] $LA = -RA - LL$,

therefore,

$$\text{left arm} = \frac{LA + LA + LA}{3}$$

$$\text{left arm} = LA.$$

Thus, if in a tracing Lead I has a T wave 3 mm. tall, and Lead III has a T wave 6 mm. tall, the amplitude of T in the left arm lead of such a case is $\frac{3-6}{3}$ or -1. $T_{left\ arm}$ is therefore downward and 1 mm. deep.*

In other words, *T_1 will be less than T_3 whenever $T_{left\ arm}$ is negative.*

In all of our twenty-five cases with the $T_1 < T_3$ pattern, we found this to be so, regardless of whether the heart was normal or abnormal. Figs. 1, 2, and 3 show typical examples of this. Fig. 1 is the tracing of a 25-year-old normal man. Fig. 2 is the tracing of a 54-year-old woman with hypertensive cardiovascular disease. The downward T waves of precordial Leads V_5 and V_6 are typical of left ventricular strain. Although T_1 is upward, notice that the left arm lead resembles precordial Lead V_6. Fig. 3 is the tracing of a 39-year-old man with anterior infarction. Precordial Leads V_2, V_3, and V_4 are typical of infarction although the standard leads appear normal. Although T_1 is upward, the left arm lead resembles Lead V_4.

Criteria have been developed to determine whether a downward T in the left arm lead is normal or abnormal.[7,9] This subject is too complex to be discussed here. However, it is important to note that all our cases with the $T_1 < T_3$ pattern showed the following: when the downward $T_{left\ arm}$ was normal or due to left ventricular strain, the precordial leads were normal or showed clear-cut evidence of left ventricular strain. When a downward $T_{left\ arm}$ was due to anterior infarction, the multiple precordial leads showed the patterns of infarction.

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*The unipolar extremity leads illustrated in this paper are "augmented," and, therefore, their amplitudes are one and one-half times larger than the actual potentials at each of the extremities. Thus, in such an example as this, the left arm lead, as recorded, would show a downward T wave, 1.5 mm. deep.[4,6]

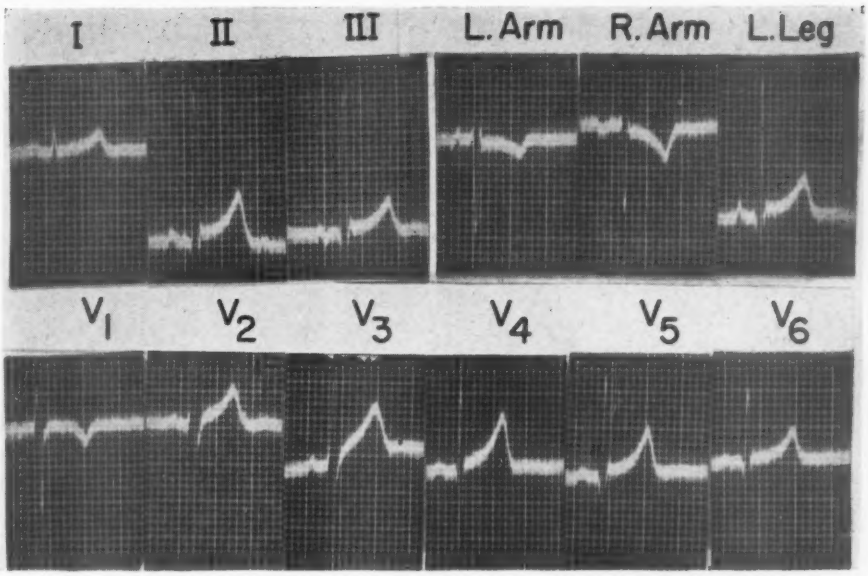

Fig. 1.—$T_1 < T_3$ pattern in a normal person.

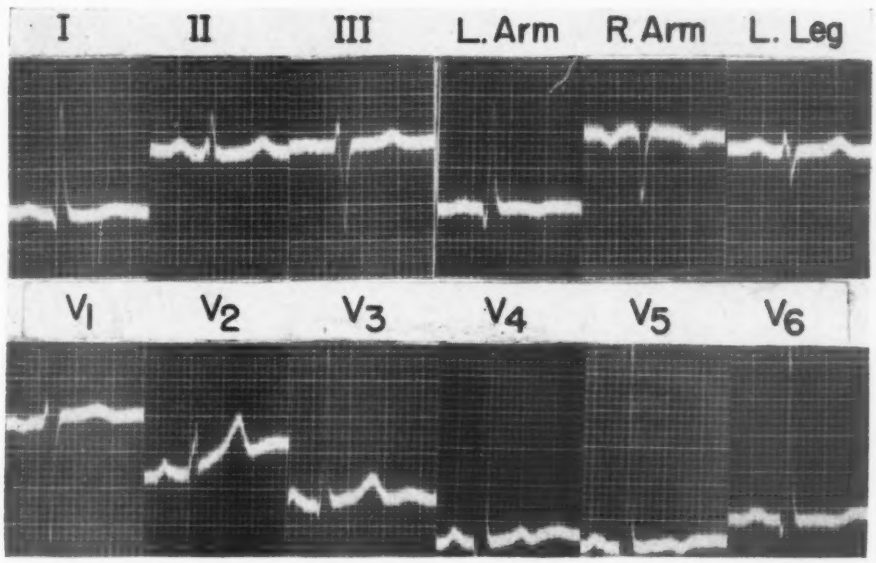

Fig. 2.—$T_1 < T_3$ pattern in a case of left ventricular strain.

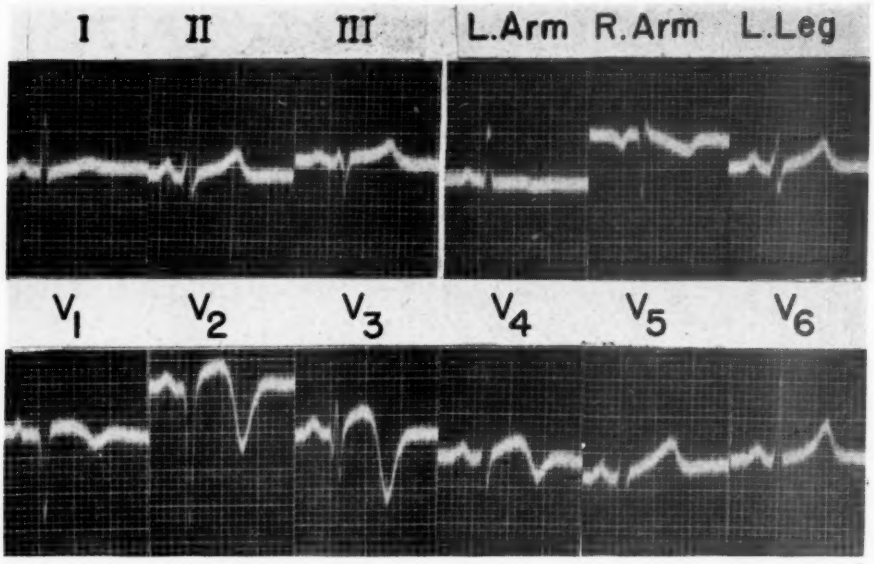

Fig. 3.—$T_1 < T_3$ pattern in a case of anterior infarction.

CONCLUSIONS

In the standard leads, T_1 may be less than T_3 in patients with anterior infarction. However, this pattern frequently occurs normally and in patients with left ventricular strain. It is due to the fact that the left arm, which takes part in the formation of both Leads I and III, shows a downward T wave in such cases.

The determination of whether the $T_1 < T_3$ pattern is normal or abnormal can be made by using multiple unipolar precordial leads. When the $T_1 < T_3$ pattern occurs normally, the multiple precordial leads are normal; when the pattern occurs after anterior infarction, the multiple precordial leads show typical patterns of anterior infarction.

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CIRCULATORY EFFECTS OF THREE MODIFICATIONS OF THE VALSALVA EXPERIMENT

An Experimental Survey

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THIS report deals with a series of experiments designed to explore three modifications of the original Valsalva experiment as a possible means of testing the circulatory adaptation to gravitational forces in applicants for pilot training. Measurements have been made of the effect of these three straining procedures on the intragastric pressure, position of the diaphragm, size of the cardiac silhouette, arterial blood pressure, finger volume, and venous pressure in upper and lower extremities.

In 1740, Valsalva reported some observations made during forced expiratory effort against the closed glottis and, since that time, various modifications of the Valsalva maneuver have been advocated as tests for different aspects of cardiovascular efficiency in response to stress. The medical literature on this subject is extremely voluminous. Liedholm[1] presented a comprehensive review of the literature up to 1939, including a large portion of the reports appearing in the European literature. The majority of the opinions presented in this survey apparently agreed that the following represent the circulatory manifestations produced during the Valsalva experiments: the heart size, stroke volume, cardiac output, capillary flow, and venous return to the heart are reduced, while the heart rate, venous pressure, and the cerebrospinal fluid pressure are increased. For a brief period after discontinuing the maneuver, the following effects have been fairly consistent: heart size, stroke volume, cardiac output, and capillary flow all were greater than normal as the distended veins became rapidly cleared of the accumulated blood. Associated with the increased stroke volume, bradycardia was usually observed. Although the direction of changes of the different variables has become fairly clear, the amount of change in each remains extremely controversial.

The systolic blood pressure during the Valsalva experiment has been reported to fall below the limits of accurate measurement. Other observations have been made which indicate that the systolic pressure progressively increases throughout the period of increased intrathoracic pressure.[1] Dawson[2] reported an increase to levels of 180 to 200 mm. Hg for a few seconds and then a precipitous fall to

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60 mm. Hg or below, followed by a gradual rise "apparently dependent upon the degree of effort." These findings have been obtained by indirect measurement of the arterial blood pressure and are thus subject to all the variability and errors associated with that method. Direct recording of arterial blood pressure during the Valsalva maneuver by means of the Hamilton optical manometer has been reported by Hamilton, Woodbury, and Harper.[3] They described four phases as follows: (a) The blood pressure rose and the pulse became slightly fuller, but the heart rate was unchanged for a few seconds after beginning the maneuver. (b) The pulmonary reservoir became depleted; cardiac filling then became inadequate and the blood pressure fell. As this phase continued, some other factor (vasoconstriction, perhaps) entered into the picture and the blood pressure began to rise gradually. (c) As the strain was discontinued the general blood pressure precipitously fell for 2 to 4 seconds. (d) Very quickly the heart filled more adequately, the pulse pressure increased, systolic and diastolic pressures increased, and the dicrotic notch mounted higher on the descending limb of the pulse curve.

It seems evident that the cardiovascular system was being subjected to a strain during the Valsalva maneuver which should aid in distinguishing individuals with inefficient cardiovascular response to the effects of gravitational forces from those with adequate adaptation. The Flack test (a modified Valsalva maneuver) has been successfully used by MacLean and his associates[4] in the demonstration of manifestations of orthostatic hypotension. The greatest difficulty in the practical application of a straining maneuver as a circulatory test has been the lack of any function which can be readily and accurately measured as a criterion of the effectiveness of the vasomotor response.

The present study was designed to explore several effects of straining procedures by means of available methods of measurement for the following reasons: (1) to attempt to establish some testing procedure which might facilitate prediction of tolerance to radial acceleration in applicants for pilot training, and (2) to gain information which might aid in understanding the mechanisms by which the cardiovascular system responds to stress.

STUDIES AND RESULTS

The Three Modifications of the Valsalva Experiment Studied.—Descriptions of the three maneuvers and symbols by which they will be identified in the remainder of the report are as follows: (a) The first maneuver consisted of increasing the intrapulmonic pressure 40 mm. Hg after a deep inspiration so that the lungs were well inflated during the strain. The symbol *Vi* is used to represent this procedure. To facilitate observation and recording of intrapulmonic pressure, the subjects were instructed to blow into a tube connected to a water manometer and to sustain a column of water 54 cm. high. This is equivalent to producing an intrapulmonic pressure of 40 mm. of mercury. (b) The second maneuver, designated *Ve*, was similar except that most of the supplemental air was exhaled prior to beginning the strain. (c) The *Ml* maneuver, originally described by Wood and Hallenbeck[5] as a means of increasing tolerance to positive radial accel-

eration, involved exhaling most of the supplemental air and then forcing air through the partially closed glottis, accompanied by vigorous tensing of the voluntary musculature. This maneuver was tested both as a single prolonged effort and also when repeated three times in rapid succession. Measurement of the increase in intrapulmonic pressure during the *Ml* procedures required that the subjects be instructed to force air through a fixed leak in the manometer system in lieu of the constricted glottis. In this maneuver the intrapulmonic pressure could be increased to 40 mm. Hg at the onset, but despite every effort the intrapulmonic pressure fell to levels of 20 mm. Hg or below as the lungs became progressively emptied.

The Effect of the Straining Maneuvers on the Position of the Diaphragm and the Size of the Cardiac Silhouette.—To observe the changes in heart size and in the position of the diaphragm, teleroentgenograms were taken on a series of subjects immediately before and during the *Vi* and *Ve* maneuvers. An automatic cassette changer ordinarily used in exposing stereoscopic chest plates was used to allow exposure of the two roentgenograms in rapid succession without changing the position of the subject.

Each subject stood facing the automatic cassette changer. The water manometer was placed in his line of vision and the metal mouthpiece on the tube leading to the manometer was held between his teeth. He took a deep breath and held it while a roentgenogram was exposed. Without inhaling or exhaling he blew into the tube, elevating the water in the manometer 54 cm. and retaining it at this level. The cassette changer was operated and after twenty seconds another roentgenogram was exposed. In this way the quantity of air within the lungs was the same during the exposure of the two x-ray films except for the gaseous interchange with the blood during the twenty-second strain. It required only 13 cm. of air to displace the fluid in the manometer which would not appreciably affect the height of the diaphragm. A similar technique was used in the study of the *Ve* maneuver except that air hunger prevented prolonged straining and the second roentgenogram was taken seven seconds after the intrapulmonic pressure was increased. In the case of the *Ml* maneuver, the escape of air from the lungs produced a progressive movement of the heart and diaphragm. The effects of this maneuver were observed by means of the fluoroscope.

To facilitate comparison of the roentgenograms taken before and during the maneuvers, tracings were made from both x-ray plates on the same sheet of paper. Landmarks such as the upper thoracic vertebral spines and the costovertebral articulations were superimposed, since these structures apparently moved very little during the respiratory movements. The areas of the two cardiac silhouettes were measured by means of a planimeter. Visualization of the cardiac border in the region of the apex of the heart was improved in several experiments by inflating the cardia of the stomach with gas in one of three ways: (a) by having certain subjects voluntarily swallow air, (b) by drinking a carbonated beverage and avoiding eructation, or (c) by injecting air through a Miller-Abbott tube when intragastric pressures were being recorded.

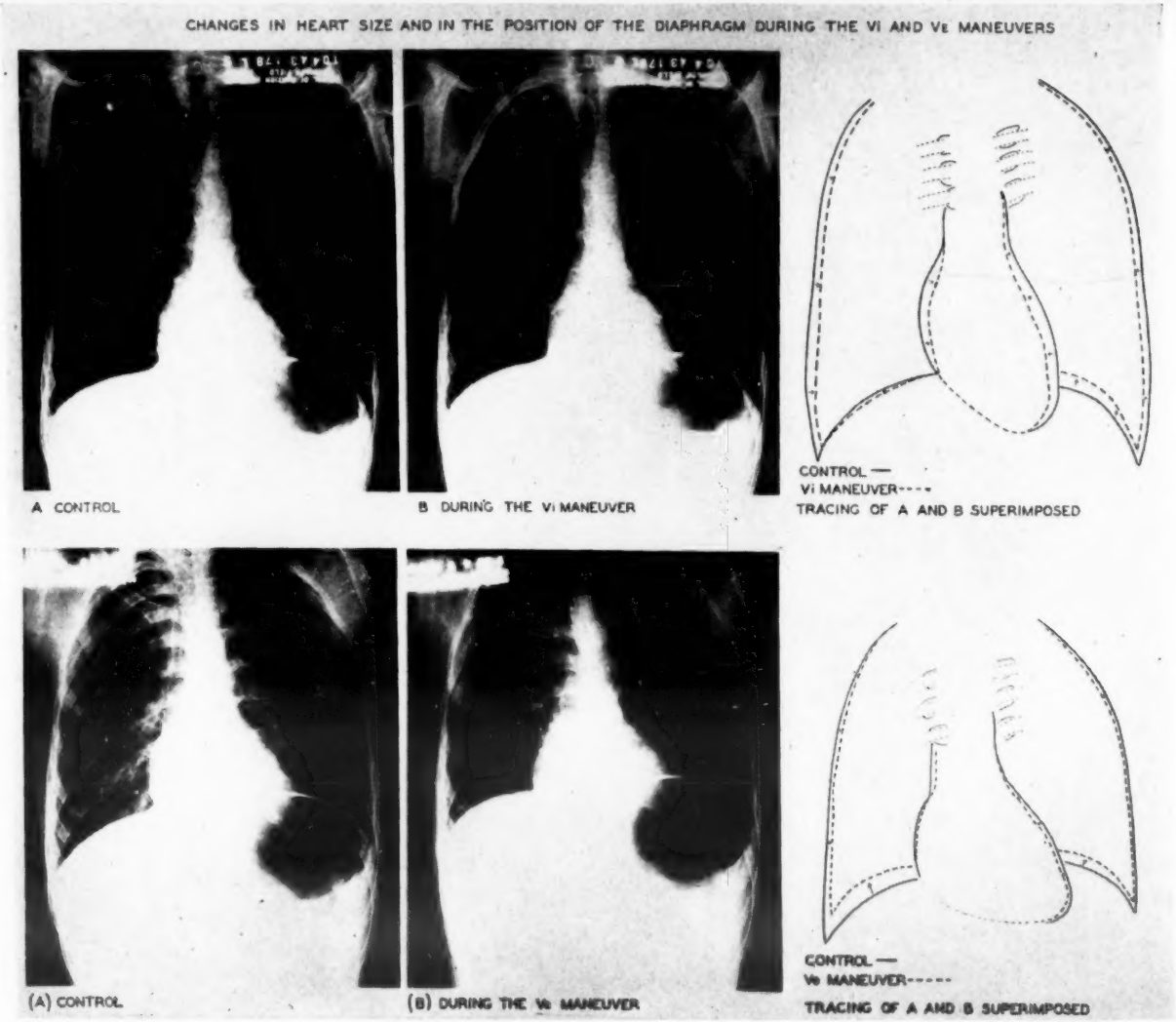


Fig. 1.—Tracings were made of the cardiac silhouette on roentgenograms taken immediately before performing the *Vi* and *Ve* maneuvers (solid line). On the same piece of paper, the cardiac silhouette was superimposed from the roentgenogram taken during the corresponding maneuver (broken line). Inflation of the cardia of the stomach with gas in several subjects facilitated observation of the cardiac border in the region of the apex.

Ve maneuvers (solid line). On the same piece of paper, the cardiac silhouette was superimposed from the roentgenogram taken during the corresponding maneuver (broken line). Inflation of the cardia of the stomach with gas in several subjects facilitated observation of the cardiac border in the region of the apex.

Results: Forty-two pairs of roentgenograms were made on thirteen healthy young male subjects. During the *Vi* maneuver, the diaphragm was elevated during the strain in about half of the cases (Fig. 1) and the area of the cardiac silhouette was decreased on the average by 20 sq. cm. (17.1 per cent). The diaphragm was invariably displaced cephalad during the *Ve* maneuver and reduction in the area of the cardiac silhouette was less marked, averaging 14.7 sq. cm. (10.4 per cent). Fluoroscopic examination during the *Ml* maneuver revealed that the diaphragm continued to move upward so long as air was expelled from the lungs. The dome of the diaphragm rose behind the heart obscuring more and more of the heart shadow. No measurements of cardiac area were attempted during this maneuver.

The Relation of Intrapulmonic Pressures to Intragastric Pressures During the Three Maneuvers.—The intrapulmonic pressure was measured by recording the pressure maintained by the subject in the manometer system by means of a Hamilton optical manometer. The various types of recording apparatus used in the present series of experiments have been described elsewhere.[6,7] Intragastric pressures were recorded by a second Hamilton manometer connected to a Miller-Abbott tube, the balloon of which was in the cardia of the stomach. The location of the tip of the tube was checked in each case by means of a flat plate of the abdomen. The intragastric pressure was always 4 to 7 mm. Hg. above atmospheric pressure and was directly affected by respiratory activity (Fig. 2). The increases in intragastric pressure during the Valsalva maneuvers were measured from the basal level which appeared during the relaxation associated with expiration. There was no evidence of interference with the accuracy of the recordings by gastric peristalis.

Results: Simultaneous recordings of the intrapulmonic and intragastric pressures were obtained during the performance of the three maneuvers by seven subjects (Fig. 2). During the *Vi* maneuver, the average increase in intragastric pressure was between 29 and 32 mm. Hg while the intrapulmonic pressure was held at 40 mm. of mercury. Since the diaphragm cannot exert force in the upward direction, it was not considered likely that the pressure in the chest could be higher that in the abdomen. The discrepency could be explained if the intrathoracic pressure were 8 to 11 mm. Hg less than the intrapulmonic pressure because of the elastic tension being exerted by the lungs. After deep inspiration the intrathoracic (intrapleural) pressure has been reported to be as much as −30 mm. of mercury.[8] During the *Ve* maneuver, the average intragastric pressure in these same subjects ranged between 45 and 60 mm. Hg (average 55 mm. Hg) when the intrapulmonic pressure was maintained at 40 mm. of mercury. Satisfactory performance of the *Ml* maneuver produced intragastric pressures of 55 to 74 mm. Hg, while the intrapulmonic pressure was gradually falling off from 40 to 20 mm. Hg, or below. The intrathoracic pressure was probably only about 2 to 3 mm. Hg less than intrapulmonic pressure due to the degree of deflation of the lungs during the *Ve* and *Ml* maneuvers.[8] The high intragastric pressures in these two maneuvers was attributed to the fact that at the beginning of the maneuver, the diaphragm was high and compression of the air within

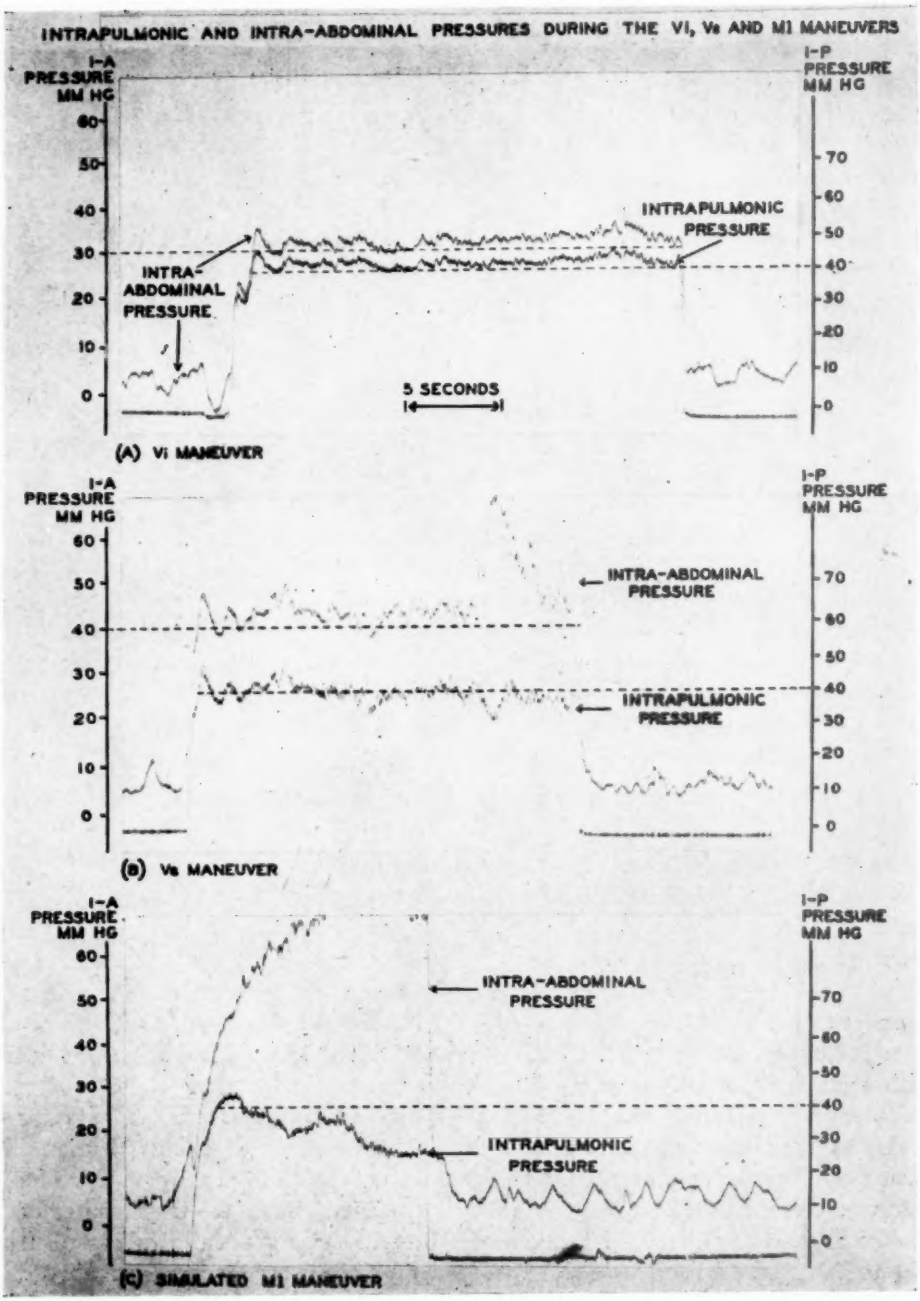


Fig. 2.—Simultaneous recordings of the intrapulmonic and intragastric pressures revealed that increasing the intrapulmonic pressure 40 mm. Hg with the lungs inflated (*Vi* maneuver) produced an increase in intragastric pressure of about 30 mm. of mercury. During the *Ve* and *MI* maneuvers, performed after forced exhalation, the intragastric pressure equaled or exceeded the intrapulmonic pressure.

the chest was accomplished by increasing intra-abdominal pressure by an amount sufficient to produce further elevation and stretching of the diaphragm. This differential in pressure between the abdomen and thorax should facilitate the flow of blood from the splanchnic venous reservoirs to the right side of the heart.

The Response of Arterial Blood Pressure, Venous Pressure, and Finger Volume During the Maneuvers.—Arterial and venous pressures were recorded on subjects in the seated position by means of a bank of Hamilton optical manometers. The intra-arterial pressure was recorded directly from within the brachial artery and the venous pressure in the arm was measured from an antecubital vein. The level at which the arm rested was adjusted in each case until the points of the intravascular needles were approximately 5 cm. below the sternal notch. Venous pressure from the dependent lower extremities was recorded from a dorsal vein of the foot or from a superficial vein in the lower part of the leg. Records were obtained of the changes in the volume of the index finger by means of simple, pneumatic, finger plethysmographs carefully fitted to the index finger. The plethysmograph was connected by small-bore rubber tubing to a rubber tambour on which a mirror was eccentrically mounted.

The arterial, venous, and plethysmographic records were obtained by photographing the deflections of the mirrors on the Hamilton manometers and finger plethysmograph tambour by means of a 12 cm. camera.[7]

Arterial pressures were recorded on sixteen subjects during one or more of the maneuvers, and in six of these venous pressures from the upper extremity were also obtained. Simultaneous records of intrapulmonic pressure, intragastric pressure, and venous pressures in the arm and leg were recorded in seven subjects. A total of seventy-three determinations of the changes in the venous pressure in the arm were made during the various maneuvers. The rate of increase in venous pressure in mm. Hg per second was calculated by dividing the amount of increase in the venous pressure by the duration of the progressive increase.

Results: Direct recording of arterial pressure during *Vi* maneuvers revealed changes similar to those described by Hamilton and co-workers.[3] An example of a typical response is presented (Fig. 3). Immediately after the maneuver was begun, the systolic and diastolic pressures increased for three or four beats. This has been attributed to the direct effect of the increased pressure within the chest on the heart and lungs. The systolic, diastolic, and pulse pressures were then reduced, presumably as a result of depletion of the blood within the pulmonary circulation and during this period the pulse rate usually increased. The gradual increase in arterial pressure during the remainder of the maneuver has been attributed to compensation on the part of the peripheral vascular system in the form of vasoconstriction. Sudden release of the intrapulmonic pressure was immediately followed by a brief but precipitous fall in blood pressure and then a very high systolic and pulse pressure associated with bradycardia. An increase in finger volume occurred during the maneuver (Fig. 3) and when the maneuver had been completed, for a period of about fifteen seconds, the volume in the finger was often less than it had been preceding the strain. This may be an indication that peripheral vasoconstriction occurred during the strain. Dur-

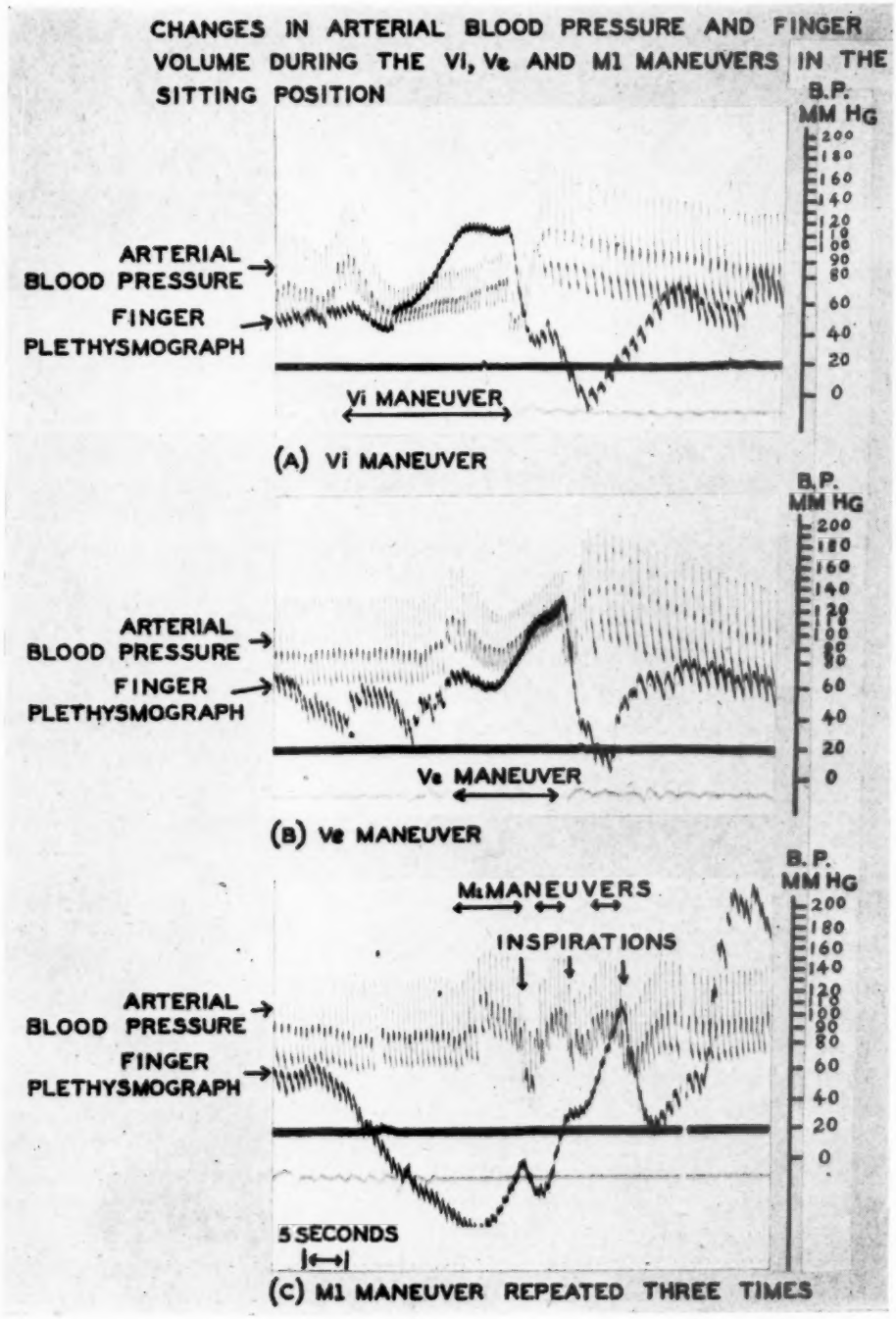


Fig. 3.—Direct arterial blood pressure, recorded by means of a Hamilton optical manometer, and changes in finger volume, recorded by means of a pneumatic plethysmograph on the right index finger, were obtained during three modifications of the Valsalva experiment.

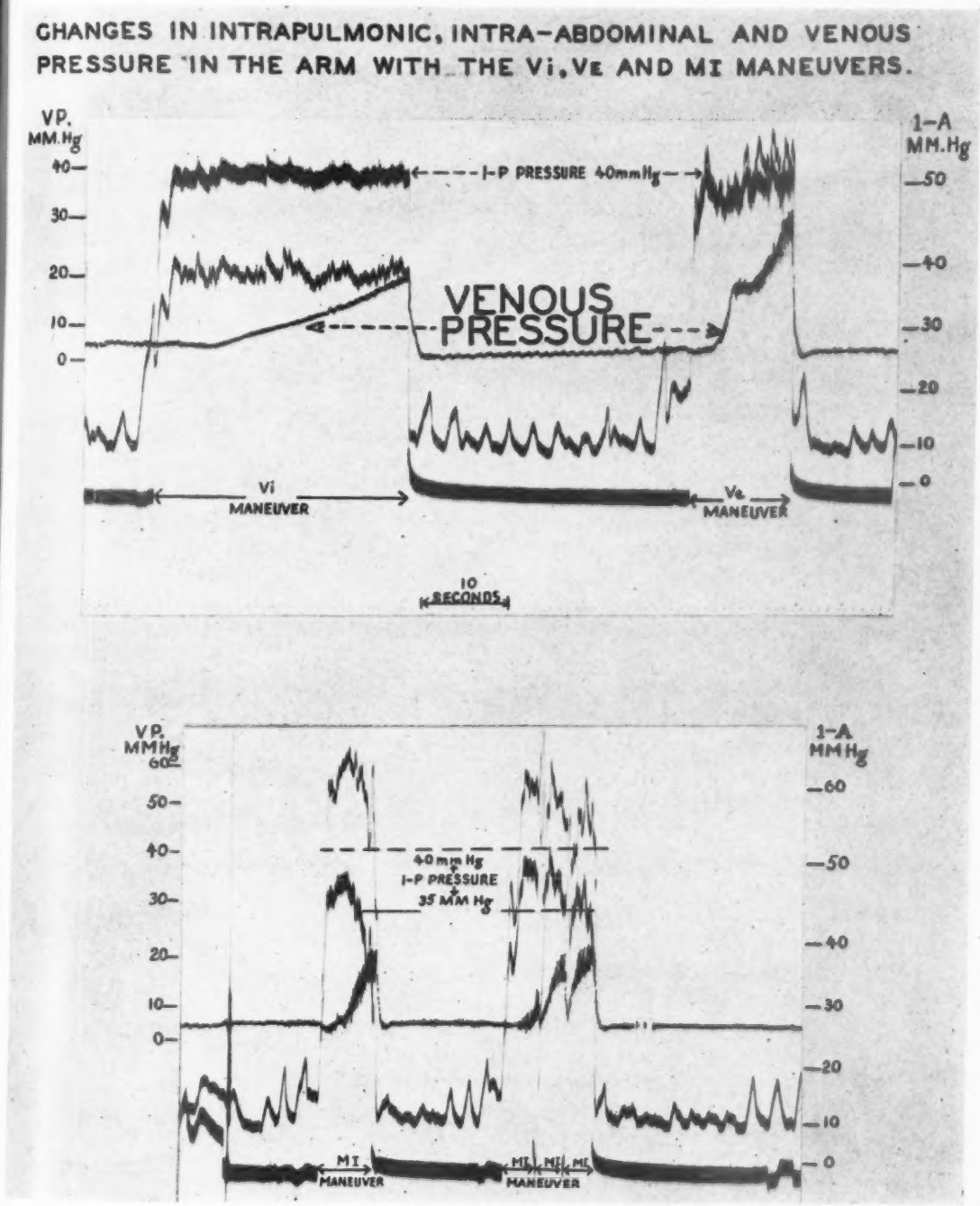


Fig. 4.—Venous pressure recordings from an antecubital vein in a seated subject during the three types of straining maneuvers in this case reveals the lag in the onset of the rise of venous pressure after the intrapulmonic and intragastric pressures were suddenly increased. The difference in the slope of the progressive increase in venous pressure during the three maneuvers is apparent.

ing the *Ve* maneuver these same changes may be identified, but the arterial blood pressure was maintained at a higher level during the strain. This may have been due to the fact that there was a gradient in pressure from the abdomen toward the thorax which provided more adequate venous return during this maneuver than during the *Vi* maneuver. *Ml* maneuvers, either single prolonged efforts or repeated efforts in rapid succession, increased the arterial blood pressure levels during the straining effort, but during the inspiratory gasps between efforts the arterial pressure fell precipitously. During these maneuvers, the finger volume increased progressively with each effort (Fig. 3).

The records of changes in venous pressure during the performance of the modifications of the Valsalva maneuver revealed a gradual increase in venous pressure when the pressure within the body cavities was suddenly increased. In the upper extremities, there was frequently a lag before the onsent of the rise in pressure (Fig. 4), while in the lower extremities the onset of the increase in venous pressure often occurred as a result of the forced inspiration or expiration preceding the actual maneuvers. This was attributed to the fact that antecubital veins at heart level were not distended with blood and required additional filling before a measurable increase in venous pressure occurred. Since the subjects were in the sitting position, the veins in the legs were probably fairly well distended with blood during the entire experimental period. Evidence in favor of this concept was found in the fact that the venous pressure in the legs varied with the changes in intra-abdominal pressure associated with respiratory activity. This was not observed in venous pressure recordings from the upper extremity.

The slope of the increase in venous pressure was usually more regular and linear during the *Vi* maneuver than during the *Ve* and *Ml* modifications (Fig. 4). The rapid oscillations occurring during the latter protion of the *Ve* and *Ml* maneuvers were due to muscular tremors associated with intensive straining. Due to the confusion resulting from having two or more records with different calibration scales appearing in a single illustration, the relation of the changes in venous pressure of the arm and leg to the increase in intrapulmonic and intra-abdominal pressure in a typical subject was illustrated by plotting these functions at two second intervals according to a single calibration scale (Fig. 5). The relation of changes in venous pressure to the pressures within the trunk are fairly typical except that venous return from the arm was probably re-established during the last portion of the *Ml* maneuver in this case. In no other experiment did the venous pressure increase exceed the pressure within the corresponding body cavity by more than 2 or 3 mm. of mercury.

The rate of increase in venous pressure during the maneuvers computed in mm. Hg per second seemed to be the most promising test used in this series. The results of this measurement can be expressed as a numerical score having some theoretical relation to the vasomotor function of the individual. Among the group of subjects studied, there seemed to be some tendency for similar results to be obtained in the same subject on repeated determinations (Table I). The possibility of standardizing the procedure seemed good and the intricacy of the apparatus does not seem prohibitive. It is important to emphasize that

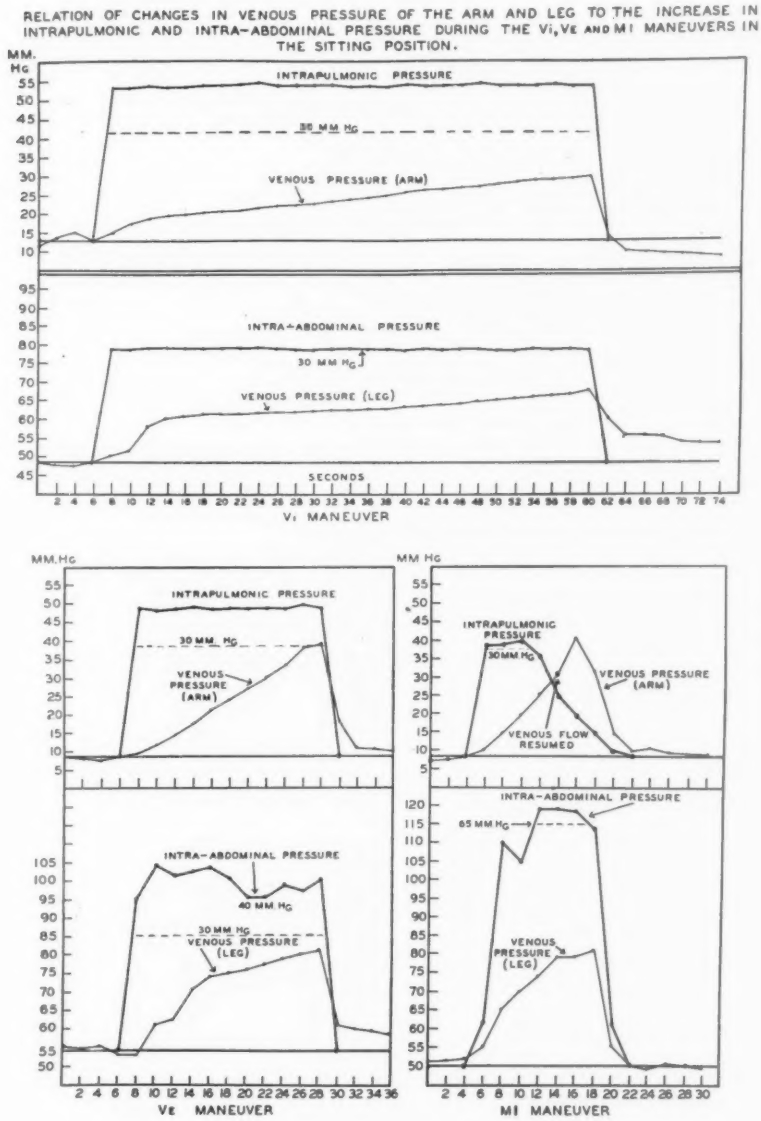


Fig. 5.—By plotting the intrapulmonic and antecubital venous pressure and intragastric and venous pressure in the lower leg at 2-second intervals according to a single calibration scale, the relation of the venous pressure increase to the pressure within the corresponding body cavity is more clearly illustrated.

in the absence of carefully conducted experiments designed to establish the reliability and validity of such a test, no reliable statement can be made concerning its usefulness.

The theoretical relation of the rate of rise of venous pressure to the vasoconstrictor function of the subject is based on the following assumptions: (1)

TABLE I. RATE OF VENOUS PRESSURE INCREASE DURING THE VI MANEUVER (ANTECUBITAL VEIN)

SUBJECT	DURATION OF MANEUVER IN SECONDS	DURATION OF VENOUS PRESSURE INCREASE IN SECONDS	VENOUS PRESSURE INCREASE IN MM. HG	RATE OF VENOUS PRESSURE INCREASE IN MM. HG PER SECOND
1	32	32	26	0.81
	32	18	27	1.50
	32	24	24	1.00
	22	22	28	1.27
2	34	34	17	0.50
	40	40	23	0.57
	36	36	25	0.70
	28	28	15	0.53
	28	28	16	0.57
3	30	30	14	0.47
	32	32	12	0.38
	36	36	10	0.28
	32	32	7	0.22
	30	30	8	0.27
4	28	28	17	0.61
	30	30	14	0.46
	32	30	13	0.43
	33	33	16	0.49
5	20	20	32	1.60
	22	22	34	1.54
	22	22	30	1.36
6	34	34	4	0.12
	30	30	5	0.17
	30	30	5	0.17
7	28	28	20	0.71
	28	28	26	0.90
8	20	16	38	2.38
	22	22	29	1.32
	22	22	25	1.14
9	26	26	7	0.27
10	26	26	23	0.89
11	56	56	17	0.30
	52	52	20	0.39
12	36	36	24	0.66
Range	20-56	16-56	4-38	0.12-2.38
Average	30.6	29.8	19.1	0.74

The presence of functional valves in normal veins prevents retrograde flow of venous blood into the extremities. This concept is substantiated by the observation that the venous pressure increased slowly when the intrathoracic and intra-abdominal pressures were suddenly elevated. (2) Under these conditions all

the blood that enters the veins has passed through the small vessels from the arterial side. (3) If venoconstriction does not occur, the rate of rise of venous pressure should depend primarily upon the rate at which blood passes through the capillaries and arteriovenous shunts. If veneconstriction occurs, this might accelerate the increase in venous pressure but may be considered a part of the vasomotor response.

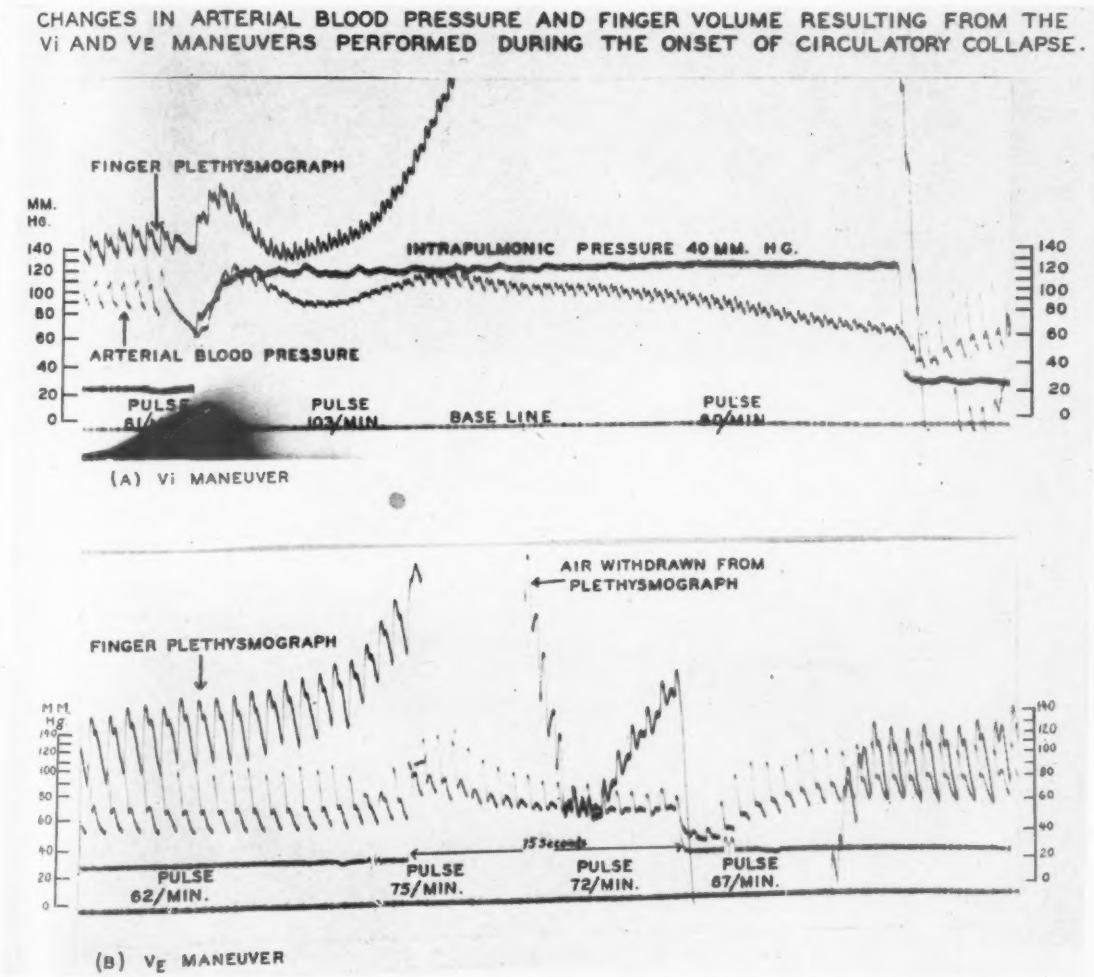
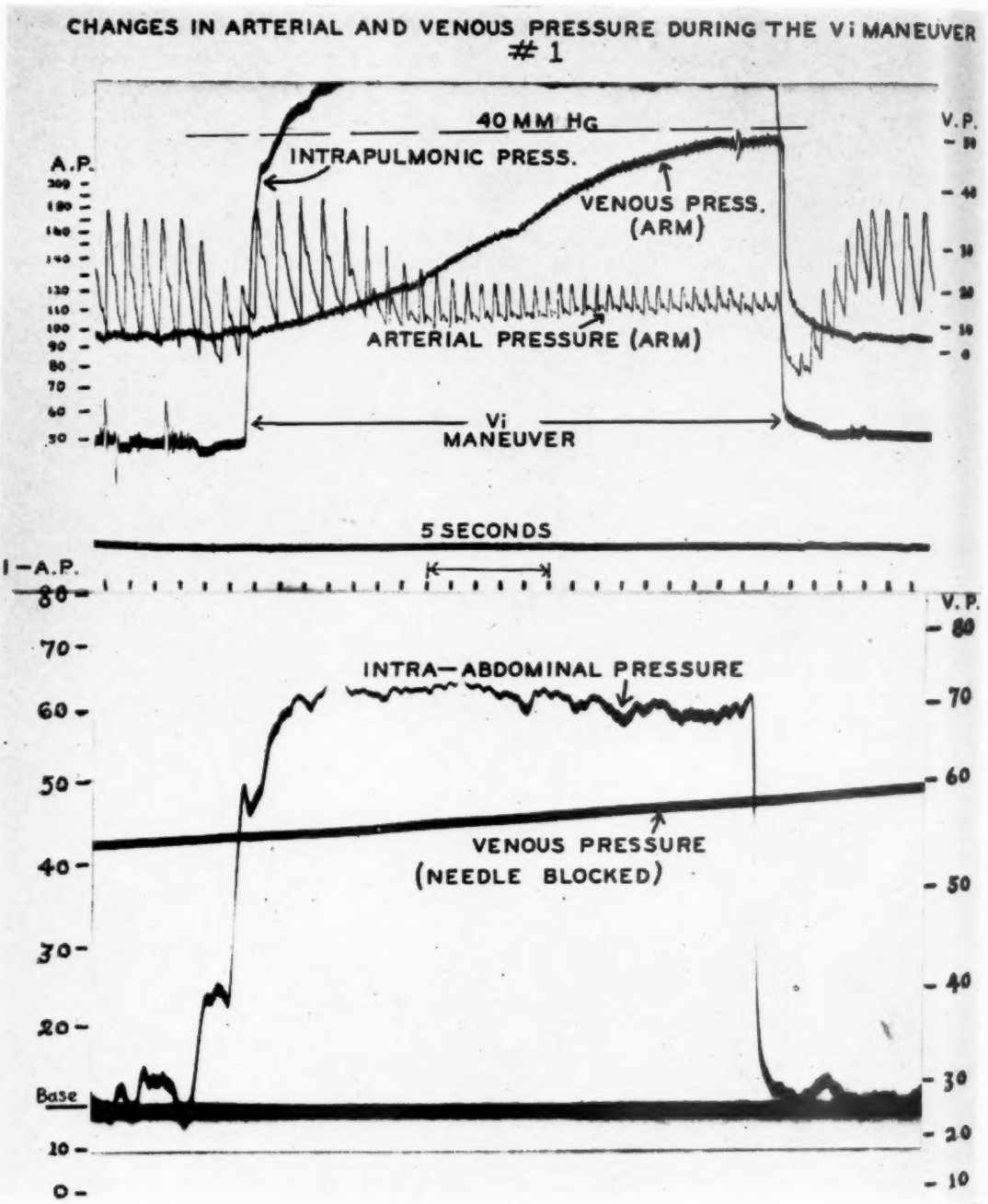


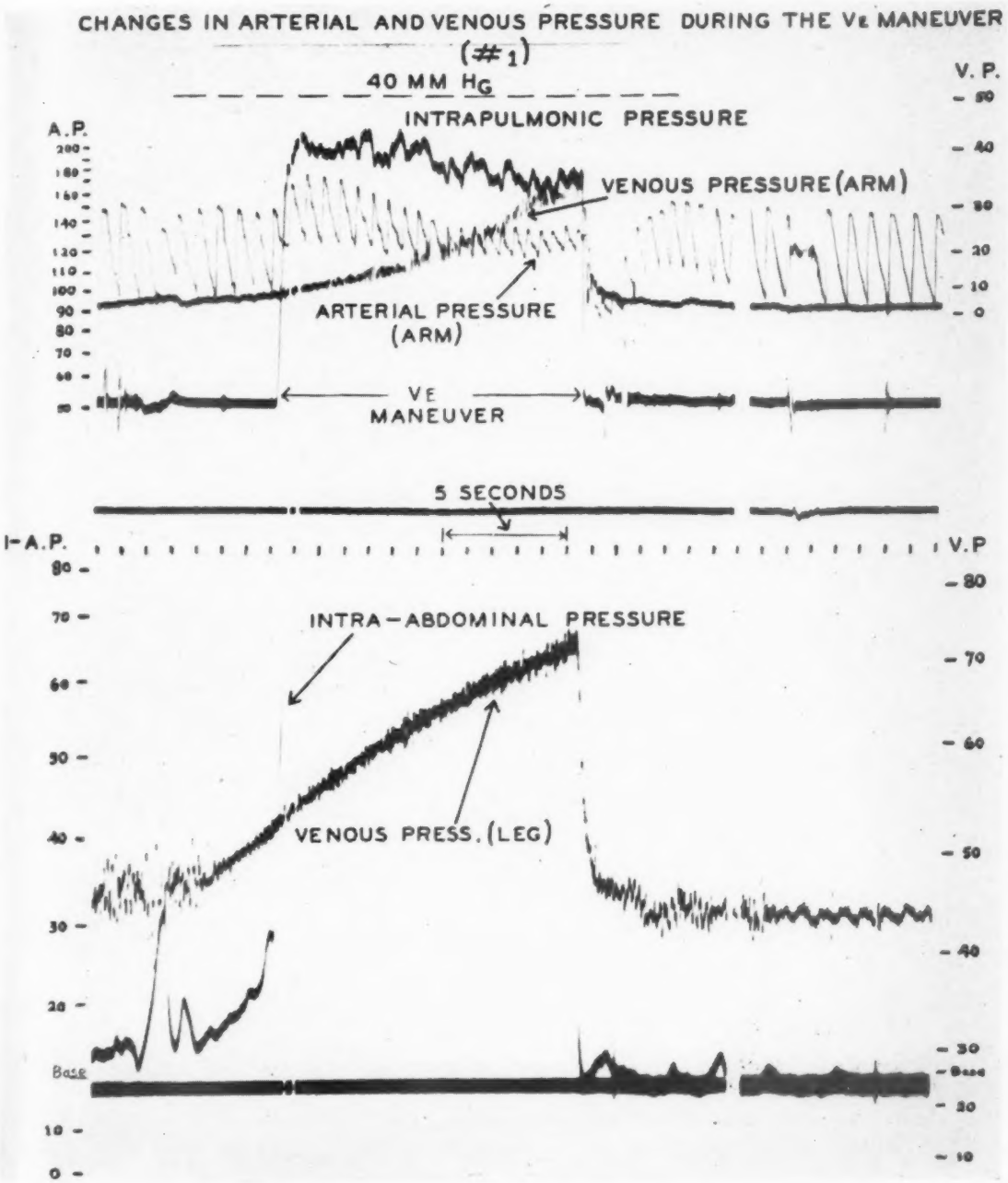
Fig. 6.—Recordings of direct brachial arterial blood pressure and changes in the volume of the index finger in a seated subject during the onset of circulatory collapse indicate the type of response seen when the circulatory adjustment during the straining maneuvers is inadequate.

Arterial and Venous Pressure Recordings in Subjects Having Poor Circulatory Compensation to Increased Intrathoracic Pressure.—In the course of this study it was possible to observe the response of fifteen subjects during circulatory



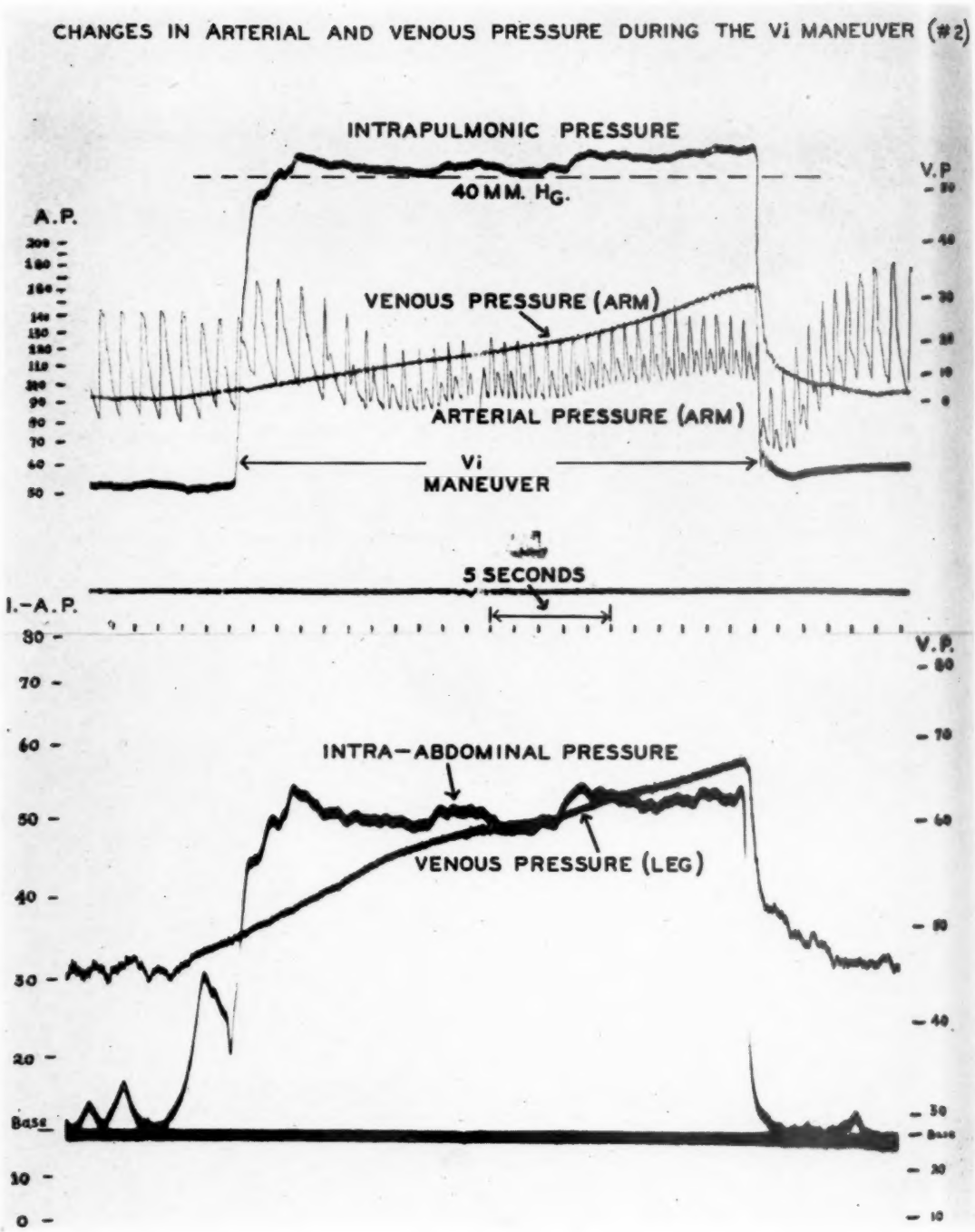
A.

Fig. 7.—Simultaneous recordings of direct arterial blood pressure, intrapulmonic and intragastric pressures, and venous pressure from the arm and leg in a subject with a history of mild orthostatic hypotension. The initial response *A* and *B*) bears marked resemblance to that revealed in Fig. 6. After three straining maneuvers had been accomplished, the response to the *Vi* and *Ve* maneuvers resembled more closely the response seen in the normal subjects (*C* and *D*).



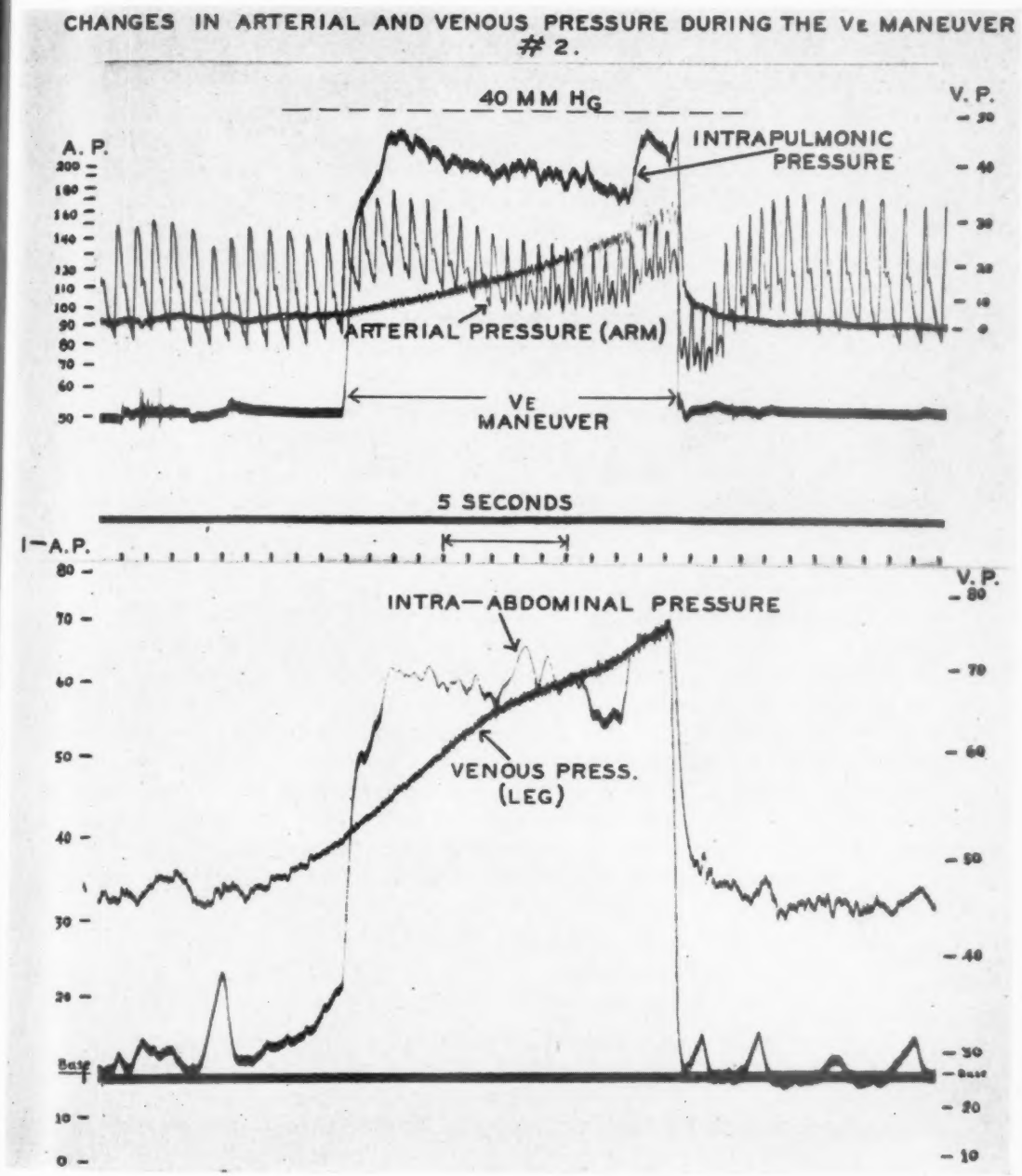
B.

Fig. 7.—For legend, see opposite page.



C.

Fig. 7.—For legend, see page 412.



D.

Fig. 7.—For legend, see page 412.

collapse apparently resulting from mechanical stimulation of the brachial arterial wall.[9] In one of these cases blood pressure recordings were obtained while the subject was performing a *Vi* and a *Ve* maneuver during the onset of the circulatory collapse (Fig. 6). In both of these maneuvers, the blood pressure response was obviously different from that previously observed in the normal subjects. The blood pressure and pulse pressure were significantly reduced and compensation during the maneuvers failed to occur. The heart rate did not increase significantly and the final systolic blood pressure was but slightly over 60 mm. of mercury. The recovery periods following the maneuvers were not accompanied by an overcompensation during which the systolic blood pressure was greater than preceding the strain. Since this subject was unable to remain erect without severe dizziness and sensation of impending loss of consciousness, it seems reasonable to classify the observed response as the result of inadequate peripheral vascular adjustment to the strain of the *Vi* and *Ve* maneuvers.

A series of interesting records was obtained on a subject having a history of occasional bouts of dizziness and loss of vision on suddenly standing erect after having been relaxed in the sitting or reclining position. On this subject, simultaneous recordings were obtained of arterial blood pressure, venous pressure from the upper and lower extremities, and intrapulmonic and intragastric pressures. A series of twelve straining maneuvers were performed during this experiment. The first two records consisted of *Vi* and *Ve* maneuvers (Fig. 7,*A* and *B*) during which the arterial blood pressure response was similar to that observed in the subject developing circulatory collapse (Fig. 6). The rate of the venous pressure increase during the *Vi* maneuver was more rapid than was encountered among the remainder of the subjects (2.38 mm. Hg per second, Subject 8, Table I). In the series of twelve maneuvers the fourth and fifth maneuvers were also *Vi* and *Ve* maneuvers (Fig. 7,*C* and *D*). The arterial response was by this time comparable to that observed in the average subject, since the pulse pressure was fairly well maintained and compensation in blood pressure occurred during the maneuvers. The rate of rise in venous pressure in the arm was obviously less than that observed during the first *Vi* maneuver.

DISCUSSION

The principal objective of the present series of studies was an attempt to devise some test of the efficiency of the cardiovascular system in compensating for the stress applied by means of modifications of the Valsalva experiment. It was assumed that individuals exhibiting poor response to such stress would also display other symptoms of inefficient cardiovascular adjustments. If it were possible to produce a satisfactory measurement of cardiovascular response to the Valsalva maneuver, this test might be useful not only in predicting tolerance to positive radial acceleration, but in general clinical practice and research. With this in mind, certain criteria were established to aid in deciding whether the methods tested might be suitable for further study or should be discarded. These criteria, which, in fact, describe an "ideal" test were as follows: (1) the measurement should be objective, preferably in terms of a numerical scale;

(2) the apparatus required to perform the test should be simple and readily available; (3) the test should be easy to perform and should not produce pain or discomfort; (4) changes in the measured function should be the direct result of the stress applied, with as few complicating factors as possible; (5) the response of various subjects should be reproducible on repeated testing of the same subjects under the same conditions; and (6) there must be a close relation between the response of the individual to the test and the state of his vasomotor system. The favorable and unfavorable aspects of the various measurements are summarized in terms of these criteria.

The Valsalva experiment is a convenient type of test because it requires only a simple manometer. The results of the experiments described previously indicated that increased intrapulmonic pressure when the lungs are well inflated (*Vi* maneuver) provides a greater stress on the circulation than the other two modifications. This assertion is based on the observed changes in cardiac size and arterial and venous blood pressure. The *Ve* and *Ml* maneuvers apparently provide a favorable gradient in pressure between the abdominal and thoracic cavities, which facilitates venous return from the splanchnic circulation.

Reduction in the size of the cardiac silhouette occurred in all subjects tested while performing the *Vi* and *Ve* maneuvers. There were obvious errors in measurement of considerable magnitude which seemed to preclude successful use of this type of measurement. For example, the magnitude of changes in the size of the cardiac silhouette in different subjects might be due to difference in the phase of the cardiac cycle at which the roentgenogram was exposed, differences in the configuration and position of the heart, and the habitus of the individual. Experience indicated that the results on repeated testing were not satisfactorily reproducible.

The records of the arterial blood pressure were probably the best available indicator of the response of the individual. Unfortunately, the changes cannot be accurately measured by means of a sphygmomanometer, the appartus required to record these changes is bulky, difficult to maintain, and unpleasant for the subject. Further, the fact that the recorded systolic blood pressure during control periods was frequently above 140 mm. Hg after the arterial puncture strongly suggested that there had been changes in the cardiovascular system due to the use of the measuring device.

The changes in finger volume during the maneuver as recorded by means of a finger plethysmograph were expected to be of some value. However, in this series the greatest difficulty was found to lie in standardization and in providing a simple but accurate measure of the volume changes.

The changes in venous pressure associated with the *Vi* maneuver offered some promise. As previously explained, the rate of increase of venous pressure during the maneuvers should be dependent in large part upon the rate at which blood passed through the small vessels from the arterial to the venous side in the extremity being tested. This measurement provides a numerical and objective result. Venepunctures are not excessively unpleasant but may affect the result through excitement or anticipation. The apparatus required is not simple be-

cause it is deemed necessary to obtain an actual record of the changes rather than depend on observing the meniscus in a venous pressure manometer. The fact that one subject revealed a rapid rise in venous pressure associated with a poor arterial blood pressure response and slow rate of increase when the response was improved is encouraging but far from conclusive.

CONCLUSIONS

1. A study has been made of the effect of three modifications of the Valsalva experiment on the size of the cardiac cycle, the position of the diaphragm, the arterial blood pressure, the venous pressure in the upper and lower extremities, and the volume of the index finger.

2. The measurements were conducted in an attempt to devise a test of the response of the peripheral circulation under stress.

3. The rate of raise of venous pressure in the upper extremity resulting from a sudden increase in intrathoracic pressure after a deep inspiration appears to have some value as a measure of the state of the small blood vessels below the point of measurement. Further study of the reliability and validity of this test is required before arriving at a decision as to its value.

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Clinical Reports

SHRAPNEL WOUND OF THE HEART WITH BENIGN MANIFESTATIONS

Involvement of the Diaphragmatic Surface of the Heart With Pain Referred to the Shoulder and Neck

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Staten Island, N. Y.

WOUNDS of the heart produce a variable clinical picture, depending on their type, size, and location. Ordinarily, in wounds of the heart the signs and symptoms of cardiac tamponade are considered. The picture is dramatic and its prompt recognition has important therapeutic implications. Not all wounds of the heart, however, are accompanied by free bleeding into the pericardial cavity, nor are they necessarily serious or fatal. A wound of the heart, regardless of its severity, which involves one of the coronary arteries may result in a fatal hemorrhage or infarction. Also, a wound of one of the auricles is particularly liable to result in uncontrolled hemorrhage. The auricle is a thin-walled chamber and has relatively less power of contractility. On the other hand, the location of the wound may be such as to present an entirely asymptomatic clinical picture. The following case report is an example of a shrapnel wound of the diaphragmatic surface of the right ventricle, confirmed by operation. This wound was at first asymptomatic, but subsequently gave rise to pain in the left shoulder and neck, presumably a referred type of pain set up by the location of the shrapnel near the left dome of the diaphragm. The patient was carefully studied six months after the operation; he was found to be in excellent health and free of complaints.

CASE REPORT

The patient was a 32-year-old white staff sergeant, with over two years' military service. His past health had been excellent. On Oct. 1, 1944, while taking part in action during the campaign around Aachen, Germany, he was struck by a piece of shrapnel from enemy mortar fire, and sustained a penetrating wound of the right anterior chest wall at the fourth intercostal space. Antishock therapy was immediately instituted, and within twelve hours he was on the operating table of an evacuation hospital. The right pleural space was aspirated. This procedure was followed by débridement and closure of the right chest wall. An exploratory laparotomy was also

From the Cardiovascular Section, U. S. Army General Hospital, Camp Butner, N. C.
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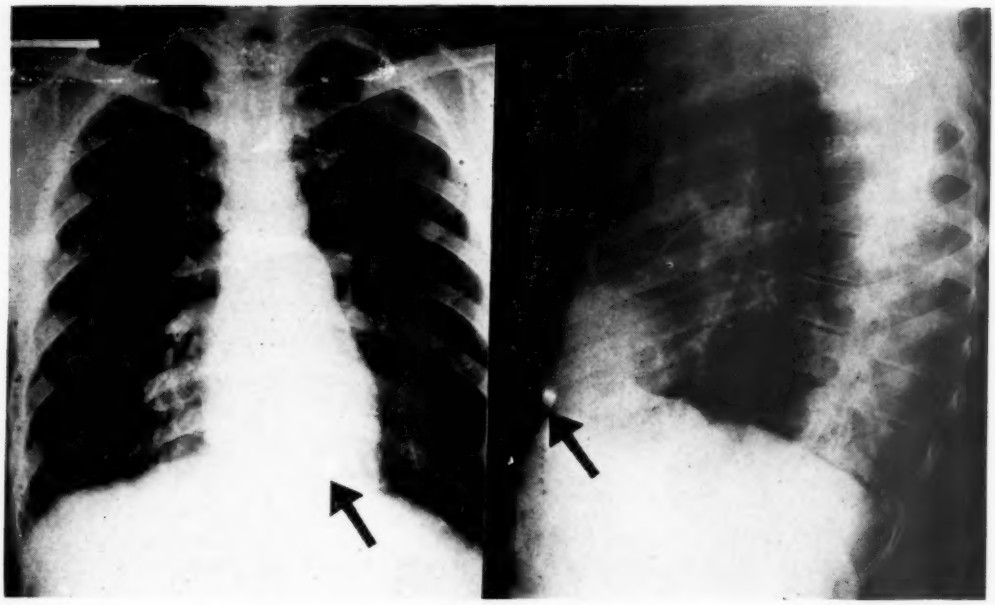

Fig. 1.—Preoperative roentgenograms of the chest demonstrating the piece of shrapnel lodged in the diaphragmatic surface of the heart.

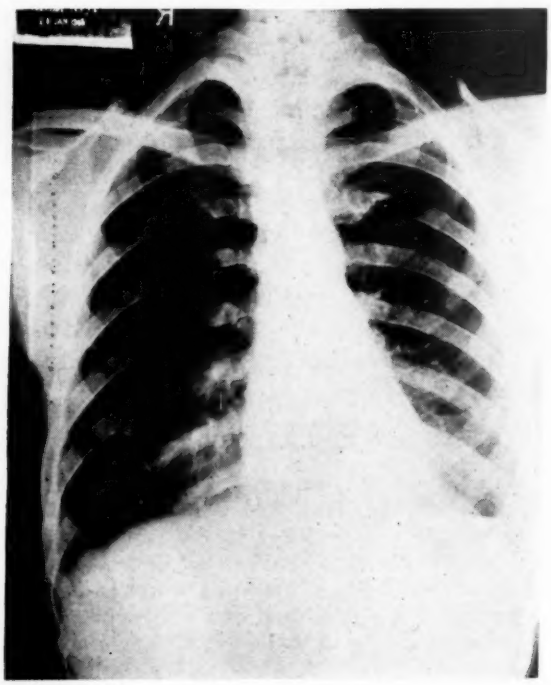

Fig. 2.—Postoperative roentgenograms of the chest taken three and one-half weeks after the removal of the piece of shrapnel shown in Fig. 3.

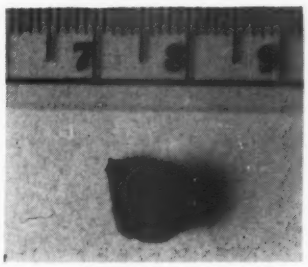

Fig. 3.—Photograph of the piece of shrapnel removed at operation from the right ventricle. The foreign body is approximately 7 x 7 x 8 millimeters.

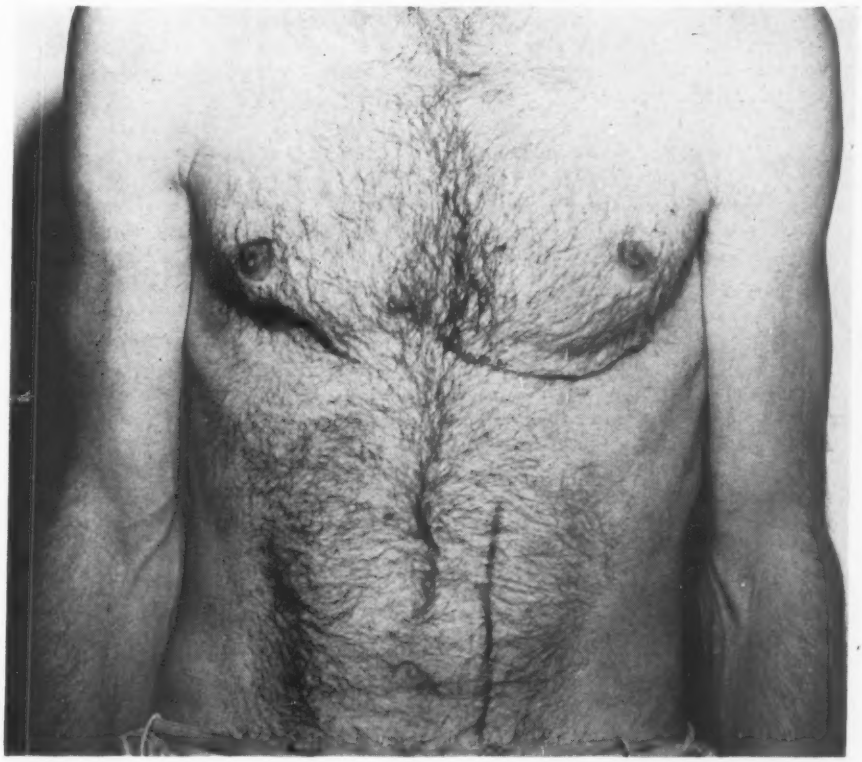

Fig. 4.—Photograph of patient taken six months after removal of the foreign body from the heart. The thinly visible scars have been outlined in pencil. The scar beneath the right nipple is the site of the original wound. The scar over the abdomen is from the exploratory laparotomy. The postoperative scar after removal of the foreign body is also shown on the left chest.

performed, but the findings were said to have been negative. The patient was then transferred through a chain of hospitals, and on Nov. 21, 1944, arrived at a general hospital in England. By this time, he was ambulatory and free of complaints. Preparations were in progress for his return to the United States. However, on Dec. 20, 1944, two and one-half months after the initial wound, he developed characteristic sharp pains in the left shoulder and neck, made worse by deep breathing. A fluoroscopic examination of the chest at that time revealed "a metallic foreign body in the region of the apex of the heart which moved with the cardiac pulsations." X-ray films taken in various positions confirmed the presence of a "metal foreign body measuring 7x8x8 mm., probably within the pericardial sac just above the diaphragm and just medial to the apex of the heart" (Fig. 1). On Dec. 26, 1944, an elective operation for the removal of the foreign body from the heart was undertaken. The operation was performed at the 140th General Hospital.*

General anesthesia was used and the following is the operative note taken from the records of the above hospital:

"The chest was opened through the fifth intercostal space anteriorly with division of the fifth and sixth cartilages close to the sternum. A segment of the sixth rib 1 cm. long, was removed laterally to facilitate exposure. The pericardium was opened laterally and readily separated from the myocardium. The foreign body was then felt just on the diaphragmatic side of the right ventricular wall 1.8 cm. medial to the anterior coronary artery running along the interventricular junction. Four silk traction sutures were placed and an incision made into the ventricular wall over the foreign body, which was removed. Moderate hemorrhage from the ventricle occurred. The myocardial wound was closed with two simple silk sutures and two traction sutures were tied over the suture line. The pericardium was closed with interrupted silk sutures except for a line 2 cm. long on the left side. The thoracic wall was closed in layers with interrupted sutures after 30,000 units of penicillin were placed in the pleural cavity. There was no significant change in pulse rate during the operation."

The patient made a remarkably prompt and uneventful convalescence (Fig. 2) and was evacuated to the United States on Feb. 26, 1945, exactly two months after the operation. It should be mentioned that the patient was entirely symptom free, but because of the unusual wound he was sent to a convalescent center, where he took part in the usual convalescent program, and at no time was he forced to limit his activities. In August, 1945, ten months from the time of the battle wound and six months after the operation, he was re-evaluated at the U. S. Army General Hospital, Camp Butner. An examination at this time revealed a sun-tanned, healthy appearing, well-adjusted soldier. When questioned about his operation, he quickly extracted from his pocket a small metallic foreign body and eagerly demonstrated "the piece of shrapnel removed from my heart" (Fig.3). Physical examination from a cardiovascular standpoint revealed no significant findings. The operative wounds were well healed (Fig. 4) and unless looked for, the scars easily escaped detection. The apical impulse was normally localized in the fifth intercostal space inside the midclavicular line. There was good expansion of both lungs; the breath sounds were normal. The heart sounds were of good quality, regular, and no murmurs were heard. The rate was 80 per minute; the blood pressure was 125/80 in the right arm and 120/76 in the left arm. The peripheral vessels were normal. Routine laboratory studies, including urinalysis, blood count, and sedimentation test, were normal. On fluoroscopic examination the cardiac silhouette appeared normal. No abnormal pulsations were seen.

Detailed electrocardiographic studies were made (Fig. 5). Standard electrocardiograms (Leads I, II, and III) showed a slight widening of the QRS complex (.11 second). Extremity studies (V_R,V_L, and V_F) revealed a pattern seen in a semivertical type of heart.[8] Precordial studies (Leads V_1, V_2, V_3, V_4, V_5, and V_6) demonstrated a pattern seen in impairment of conduction of the right bundle branch.[4,8] Application of the exploring electrode† over the ensiform region

*The operation was performed by Lt. Col. George N. J. Sommer, Jr., Medical Corps, Army of the United States, and the assistants were Lt. Col. Clyde W. Everett, Medical Corps, and Capt. Charles E. McColloch, Medical Corps, Army of the United States. The anesthesia was administered by Capt. Phyllis Conley, Army Nursing Corps.

†In these studies the central terminal electrode technique was used.

(V_E) and over the right upper quadrant in the midclavicular line beneath the costal margin, *RUA*, revealed a characteristic, widened M-shaped type of QRS complex. An esophageal tracing, *E*, taken at the level of the ventricle (50 cm.) showed a Q wave of .3 to .4 mv., and a widened QRS complex. The Master two-step exercise test gave normal findings.

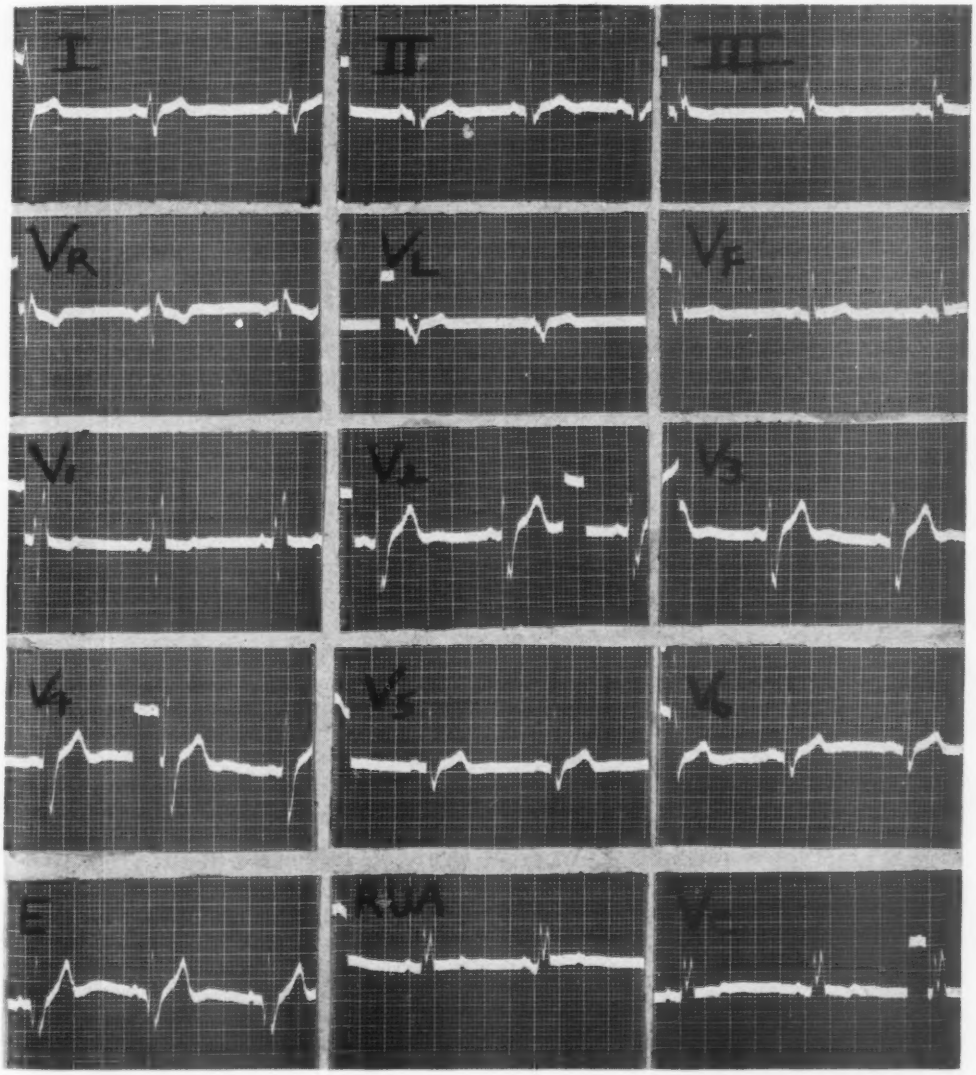

Fig. 5.—Upper row (Leads I, II, and III) shows the electrocardiograms of the three standard leads. The second row are extremity studies: right arm, (V_R); left arm, (V_L); and left foot, (V_f). The third and fourth rows are precordial studies. *E* is an esophageal tracing taken at the level of the ventricle (50 centimeters). Lead *RUA* was taken with the exploring electrode over the right upper quadrant in the midclavicular line beneath the costal margin. V_E is a tracing from the ensiform region. In these studies the central terminal electrode technique was used. For discussion, see text.

DISCUSSION

The symptomless feature of foreign bodies embedded in the heart is not new, and has been commented upon by others.[3,5,7] The frequent incidental finding at autopsy of long existing foreign bodies in the heart clearly testifies that no symptoms need occur because of their presence. Experimentally, ordinary stimuli applied to the heart give rise to no painful sensation. The heart like the liver and the intestine, may be traumatized, cut, or burned without evidence of pain.[1] The classical reference to the insensitivity of the surface of the exposed heart was Harvey's demonstration of this phenomenon in the exposed heart of Viscount Montgomery.[1] Silverman and Cove[6] reported a patient in which a bullet had been embedded in the heart musculature for forty-one years. This patient was asymptomatic and the bullet was localized by the roentgenkymograph.

Not all foreign bodies, however, are asymptomatic. Once implantation of a foreign body takes place, inflammatory changes may follow.[3] These changes may act as foci of irritation to adjacent structures such as nerves, pleura, and diaphragm. In view of Capps' work,[2] the complaint of pain in the region of the left shoulder and left side of the neck in our patient is of experimental and clinical interest. The location of the shrapnel, accurately confirmed at operation, was unique. The piece of shrapnel entered the right chest, traversed the right lung and strategically lodged itself in the musculature of the diaphragmatic surface of the right ventricle adjoining the central portion of the diaphragm (Fig. 1). Capps[2] has shown that the sensory supply of the diaphragmatic pleura is derived from two sources, the phrenic nerve which innervates the central portion of the diaphragmatic pleura, and the last six intercostal nerves which innervate the outer portion of the diaphragmatic pleura. Experimental irritation of the central portion of the diaphragmatic pleura gave rise to a true referred pain in the corresponding neck and shoulder region, the impulses travelling by way of the phrenic nerve trunk to reach the third and fourth cervical spinal segments. It is interesting to note that our patient was free of symptoms until two and one-half months after the initial wound, at which time he developed the pains in his neck and left shoulder region, made worse by deep breathing. During this period, apparently, involvement of the diaphragmatic pleura was minimal. It is a well known clinical fact that changes involving the surface of the heart and pericardium may be extensive but unless the adjoining pleura is involved no appreciable pain may be experienced.[2]

Electrocardiograms taken on patients with wounds or foreign bodies embedded in the heart musculature may be perfectly normal. In this respect, not all myocardial infarcts produce changes in the electrocardiogram. The region involved cannot always be explored by the various positions of the electrodes. Furthermore, cardiac wounds are usually small and often little of the musculature is involved. Where there is severance of the conduction system, however, the changes are quickly and easily registered in the electrocardiogram.

The electrocardiographic tracings in our patient are interesting. There is little doubt that the electrocardiograms display abnormalities in both the chest and limb leads which are usually ascribed to right bundle branch block.[4,8] With-

out a preoperative electrocardiogram for comparison, it is impossible to determine whether the shrapnel or the postoperative myocardial scar caused these changes, since such defects in conduction are encountered, at times, in young subjects who show no other symptoms or signs of organic disease.

SUMMARY

1. A case is presented of a soldier who had a shrapnel wound of the heart and was asymptomatic except for referred pain in the left shoulder and neck region.

2. The foreign body was accurately localized and successfully removed at operation. It consisted of a piece of shrapnel 7 x 7 x 8 mm. which was embedded in the musculature of the diaphragmatic surface of the right ventricle.

3. Foreign bodies of the heart may be asymptomatic and, unless adjacent structures such as the diaphragmatic pleura are involved, no symptoms need arise.

4. The patient was carefully studied less than a year after being wounded and six months after the operation. He was found to be in excellent health and, except for some interesting electrocardiographic changes, there was no objective evidence of cardiac impairment.

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ASYMPTOMATIC CONGENITAL COMPLETE HEART BLOCK IN AN ARMY AIR FORCE PILOT

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CASES of congenital complete heart block have been reported in sufficient numbers to make the condition well known to the cardiologist, if not to the general practitioner. This case of heart block in an Army Air Force pilot is reported because it emphasizes in a striking way the benign course that such a disease may take, and suggests that, as in many other cardiac arrhythmias, the ultimate prognosis in heart block is dependent on the nature and the progressiveness of the underlying cardiac disease and not on the arrhythmia itself.

CASE REPORT

A 24-year-old Army Air Force bomber pilot was admitted to Mitchel Field Regional Station Hospital on May 26, 1946, for evaluation of a bradycardia discovered during a routine physical examination. He was entirely asymptomatic.

The patient was born Sept. 20, 1921, a normal infant as far as can be determined at this date. He was not cyanotic and required no resuscitation. At the age of 10 days he had a mild short-lived episode of respiratory distress, the nature of which cannot now be determined. As a child the patient had uncomplicated measles, mumps, and chicken-pox, and suffered no sequelae. At the age of 5 years he had a mild attack of pnuemonia, also without known complications or sequelae. He had occasional sore throats, none of which were very severe. A tonsillectomy was performed at the age of 7 years. He never had any of the symptoms or signs of acute rheumatic fever, diphtheria, or scarlet fever. He denied having had any venereal disease. When 8 years of age, during a minor upper respiratory infection, he was examined by the family physician who told his mother that he had a slow pulse rate, but that it was normal for him and that he had always had it. Family history, as given by the patient, revealed no known cardiac anomalies or arrhythmias, and no known familial disease tendencies.

As a youth he indulged vigorously in all activities and sports without symptoms of any kind. He denied specifically ever having fainted or suffered a convulsive seizure, or ever having had chest pain, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, dependent edema, or palpitation.

He was inducted into the Army July 7, 1942. During his Army career he had numerous physical examinations, including many by the Flight Surgeon's office. His pulse was variously reported during this period as ranging between 48 and 80 resting, and 60 and 110 beats per minute after exercise. It was also stated that the heart rate always returned to the resting level within two minutes. On several occasions a systolic murmur was heard at the cardiac apex. This was always considered to be functional. He became a Flight Cadet in April, 1943, and went through the very strenuous physical training that this course entails. He recalled having covered a cross-country course with unbroken running over the period of an hour with less discomfort than most of his fellow trainees. He was trained as a four-motor pilot and was sent overseas in 1944, as

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the co-pilot on a B-24 Liberator Bomber. He completed ten missions, flying over 20,000 feet at low oxygen tensions with no ill effect. On the last mission his plane was hit by flak over Munich and was forced down in Switzerland. At no time did he suffer any traumatic injury during his stay in the Army. On his return to the United States the bradycardia was again noted at Fort Devens and an electrocardiogram was taken. This revealed complete heart block with auriculoventricular dissociation. He was sent to Westover Field and then to Mitchel Field Regional Station Hospital for further evaluation.

Examination revealed a well-developed slender white man, 5 feet, 11 inches in height, weighing 155 pounds, who appeared neither acutely nor chronically ill. Head, eyes, ears, nose, and throat were all normal. There was no lymphadenopathy; the thyroid gland was barely palpable. The chest was asthenic and symmetrical. The lungs were clear to auscultation and percussion. Blood pressure was 110/60. Resting pulse rate was 40 per minute, regular, and of good quality; immediately after vigourous exercise, it rose to 72 per minute and was still regular. Two minutes after exercise it was again 40 per minute. The change between these rates was gradual. All peripheral pulses were normal. The strongest pulsations in the neck were observed to correspond with the peripheral arterial pulse. Although they could not be accurately counted, smaller, more frequent venous pulsations could be seen; sometimes superimposed on the arterial pulsations, sometimes irregularly spaced between the arterial pulsations. The apex beat was felt in the fifth intercostal space, 9 cm. from the midsternal line. There were no thrills or abnormal thrusts palpable. The heart sounds were of good quality, but the first heart sound at the apex seemed to vary in intensity from beat to beat. The second aortic sound was of the same quality as the second pulmonic sound. There was a Grade 2, blowing systolic murmur heard best within the apex, radiating medially and upward. This murmur was loudest when the patient was in the supine position. There was no diastolic or presystolic murmur, but irregularly, after every few heart beats during the diastolic phase, an extra heart sound could be heard. The abdomen was flat, nontender, and no organs were palpable. All superficial and deep reflexes were equal and active. The remainder of the physical examination was negative.

Laboratory examination revealed a normal red cell count of 4,950,000 erythrocytes, hemoglobin 94 per cent, and 7,400 white blood cells with a normal differential count. Sedimentation rate (Westergren) was 3 mm. in one hour. Urine was normal. The Kahn test was negative. The arm-to-tongue circulation time (calcium gluconate) was 12 seconds. Teleroentgenogram (Fig. 1) and cardiac fluoroscopy revealed no abnormality in size and shape of the heart. There was no individual cardiac chamber enlargement.

The electrocardiogram (Fig. 2) taken with patient at rest revealed complete auriculoventricular dissociation, with an auricular rate of 74 and a ventricular rate of 42 per minute. There was a slight auricular arrhythmia. The time between successive P waves was regularly shorter when a QRS complex comes between them than when there is no intervening QRS complex. (This auricular arrhythmia in heart block was most recently discussed by Parsonnet and Miller, 1944.[1]) There were no axis deviation or abnormalities other than the dissociation.

The effects of exercise, full inspiration and full expiration, a hypodermic injection of 1 c.c. of 1:1,000 epinephrine hydrochloride, and of 1 mg. atropine sulphate were tried and recorded electrocardiographically. At no time was there a change in degree of heart block. Slight nervousness and palpitation were felt after the injection of adrenalin, but no other symptoms were noted. The exercise consisted of hopping in place for one minute. With the exception of exercise, the other procedures produced only a moderate effect on the auricular rate, and almost no effect on the ventricular rate. This is shown in Table I.

In view of the lack of history of rheumatic fever, diphtheria, syphilis, trauma, or other predisposing illness, and in view of the history of bradycardia during early childhood, the heart block in this case is probably congenital in origin and probably associated with an interventricular septal defect. The relatively normal pulse rates recorded in some of his past Army physical exami-

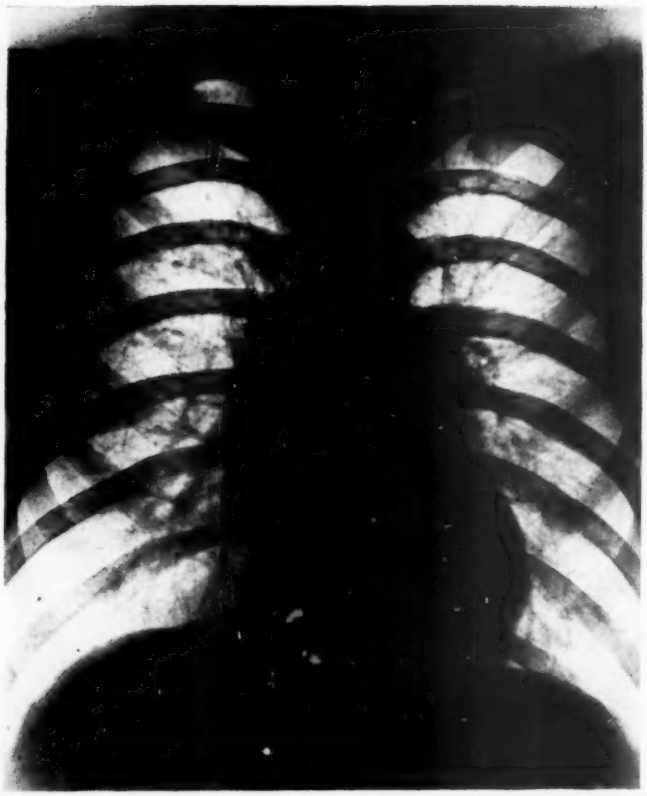

Fig. 1.—Teleroentgenogram of an Army Air Force pilot with asymtomatic congenital heart block.

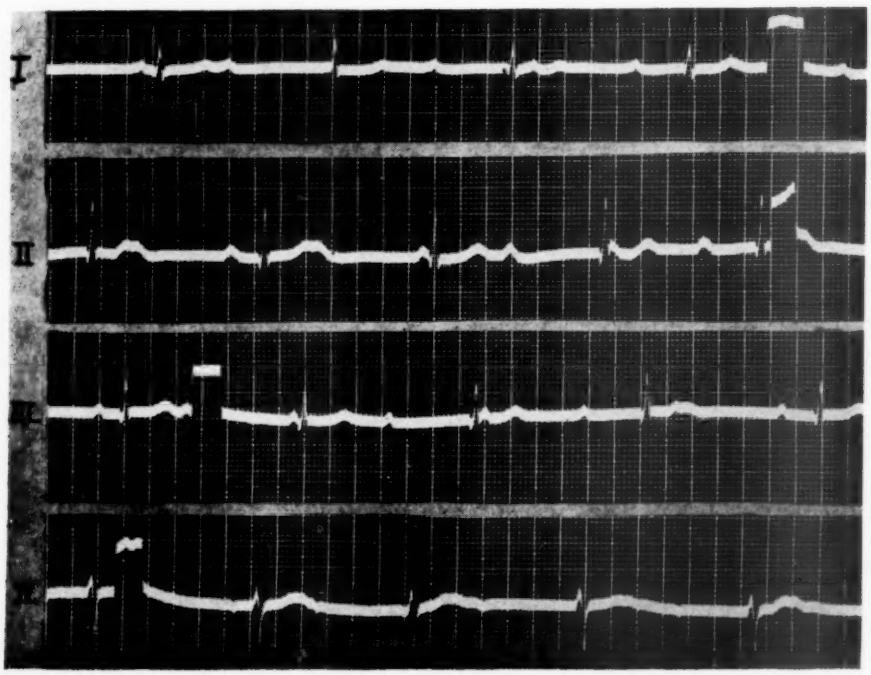

Fig. 2.—Electrocardiogram revealing the presence of complete A-V dissociation in an Army Air Force pilot.

TABLE I. THE EFFECT OF VARIOUS PROCEDURES ON THE AURICULAR AND VENTRICULAR RATES AS DETERMINED ELECTROCARDIOGRAPHICALLY

	AURICULAR RATE	VENTRICULAR RATE
Supine, at rest	62	40
Immediately after exercise	85	50
10 minutes after adrenalin	72	43
20 minutes after adrenalin	65	41
30 minutes after atropine	75	41

nations were probably the result of hurried examinations carried out in mass programs where pulse rates were freqently taken by enlisted men with little training.

DISCUSSION

Approximately 100 cases of congenital heart block have been recorded in the literature. The condition has been discovered and the diagnosis has been made most often during infancy and childhood. However, it has been diagnosed several times in utero[2] from the discovery of an otherwise unexplained fetal bradycardia; many times it has not been diagnosed until discovered for the first time during adulthood and middle age.

In a frequently quoted review, Yater[3] in 1929 listed the following criteria as essential for the diagnosis of congenital heart block: (1) established block in a young person proven by graphic methods, (2) evidence of history of bradycardia at an early age, (3) absence of a history of any disease such as diphtheria, acute rheumatic fever, chorea, or syphilis which would be likely to leave permanent cardiac stigmata in a young person. He also listed as helpful in making a diagnosis two further criteria; (4) a history of syncopal attacks or convulsive seizures, and (5) presence of other signs of congenital heart disease, particularly of patent interventricular septum.

In addition to these criteria it should be mentioned that the ventricular rate is likely to be faster in congenital heart block where it usually ranges between 40 and 50 than it is in acquired heart block where it usually ranges between 30 and 40 per minute. Campbell[4] points out that this relatively fast rate in congenital heart block frequently causes it to be overlooked in routine physical examinations. The relative frequence of congenital heart block as compared with acquired heart block is reflected in Campbell's statistics.[5] He studied seventy-four cases of permanent complete heart block and concluded that ten cases, or 13 per cent, were congenital. He found also that eighty-four per cent of the cases of acquired heart block occurred after the age of 50 years. Thus, in the younger age groups at least half of the cases were presumably congenital in origin.

The possible etiology of congenital heart block has been discussed many times. However, the paucity of histologic material makes the discussion largely speculative. It is known that the most common associated congenital defect is a patent interventricular septum. In a case studied microscopically by Yater, Lyon, and McNabb,[6] a defect in the interventricular septum was seen to com-

pletely separate the A-V node from the bundle of His. However, it is unlikely that this is frequently the cause of heart block because the conducting fibers embryologically develop before the septum and usually run posterior to the site of the ventricular defect.[7] In addition, cases of heart block have been reported with intact ventricular septa, and cases of only partial block with complete absence of the septum. The histologic findings of Yater[3] and of Yater, Leaman, and Cornell[8] who found complete separation of the A-V node from the A-V bundle by the central fibrous body, and of Wilson and Grant[9] and others who found areas of fibrosis, noninflammatory in character, which infiltrated and encroached on the conduction system, suggest that congenital heart block is usually the result of an inherent defect in the development of the conduction system occurring independently, though often in conjunction with other congenital defects.

The great majority of cases reported have not been free from cardiac symptoms or from the various stigmata of cardiac disease. For example, of the thirty cases reported by Yater, twenty-eight had varying degrees of cardiac enlargement with mild to severe degrees of cardiac disability, and fifteen of these cases had some degree of cyanosis.

However, there have been several cases reported in normal healthy adults. Jaleski and Morrison[10] in 1943 reported two cases of congenital heart block in healthy adults. One of them, a 20-year-old woman, was always in good health, worked in a sedentary position, but did complain constantly of easy fatigue and weakness. The other patient, a 31-year-old woman, was well and had undergone two pregnancies with little difficulty, but two years after the second pregnancy, during a period of considerable strain, had several fainting episodes suggestive of Adams-Stokes seizures. Both patients had murmurs suggesting a patent interventricular septum. Roentgen-ray examination of their hearts showed them to be normal in size and shape.

Smith[11] in 1921 reported the case of a 21-year-old man with complete heart block who had episodes of fainting between the ages of 3 and 9 years. These had disappeared and the patient at the time of the report had no disability from strenuous athletic exercise. His heart was slightly enlarged. His pulse rate averaged 42 per minute but, interestingly enough, rose to 58 with a regular sinus rhythm during complete expiration; his ventricular rate rose to 64 after exercise and to 56 per minute after atropine.

Davis and Stecher[12] mention a case, described by Callandré, of a 21-year-old man who withstood strenuous exercise without discomfort. He had complete heart block except when he was at complete rest, at which time he developed a regular sinus rhythm with a P-R interval of less than 0.2 second.

Campbell[4] in 1943 reported a very interesting group of seven cases of complete congenital heart block varying in age between 22 and 42 years. All were well and led active normal lives. Four of these cases were men, one on active duty in the Royal Air Force as a ground electrician though he actually "passed for flying duties." Of the three women all were well and asymptomatic. The oldest who was 42 years of age was doing housework on a farm; the other two led more sedentary lives, partly because of easy fatigability and partly because

their doctors discouraged more activity. Only one of these patients had a history of Adams-Stokes attacks. All had x-ray evidence of slight cardiac enlargement and had murmurs suggesting patent interventricular septa.

The patient presented in this report fulfills Yater's criteria for the diagnosis of congenital heart block. Because of the complete absence of any symptoms and his ability to withstand the rigors of Air Force training and high altitude combat missions as well as or even better than many of his fellows, he passed through three and one-half years of Army life and underwent many routine physical examinations before it was decided to investigate his bradycardia. The A-V dissociation in the electrocardiogram, the nature of the heart sounds, and the systolic murmur which suggested a patent interventricular septum were the only positive findings. There was no evidence at all of any impairment of cardiac efficiency.

Although there have been only a few cases of asymptomatic congenital heart block reported in adults, those that have been followed up have continued to do well and to lead normal lives without developing noteworthy symptoms or having minor disabilities progress. It is felt, therefore, that the ultimate prognosis in the case presented here, and in similar cases, is excellent. This patient was advised to try to forget that doctors had discovered something wrong with his heart and to continue to take a normal part in all activities. He was urged, however, to avoid exerting himself to the point of exhaustion.

SUMMARY

1. A case of complete congenital heart block occurring in an asymptomatic Air Force pilot which escaped discovery during three and one-half years of active service in the Army has been presented.

2. The incidence of congenital heart block, the incidence of symptom-free cases, and their ultimate prognosis has been discussed.

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OBSERVATIONS ON BERIBERI HEART DISEASE

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THE modern classical concepts of beriberi heart disease, first defined by Wenckebach[1,2] and later elucidated by Weiss and Wilkins,[3] are now undergoing revision. Blankenhorn and associates[4,5] have made important recent contributions to our knowledge of the condition. Although the application of their criteria makes earlier diagnosis possible, these authors point out that many fundamental questions still remain unanswered. Solution of these problems will enable really early recognition of the condition and the institution of therapy in the incipient stages of the cardiovascular disturbances associated with beriberi. Such information also will be of value in recognizing cardiovascular effects of thiamine deficiency superimposed on organic heart disease[6] or complicating prolonged febrile disorders.[7] Likewise, it has long been felt that many of the cardiovascular disturbances accompanying thyrotoxicosis may well be explained by inadequate thiamine supply in the face of the markedly increased demand necessitated by the hypermetabolism of this condition. Many of the basic physiologic disturbances are similar in both states. Revised criteria may well aid in this regard.

The traditional diagnostic signs of Aalsmeer and Wenckebach,[8] later substantiated by Weiss[9] and by Weiss and Wilkins,[3] include abnormally rapid circulation, prominent right heart, "pistol shot" arterial phenomena, gallop rhythm, syncope or shock, and critical improvement after specific treatment. By the application of these criteria alone many cases will be overlooked. Blankenhorn's[4] revision of the findings necessary for diagnosis include enlarged heart with normal (sinoauricular) rhythm, elevated venous pressure, peripheral neuritis or pellagra, nonspecific changes in the electrocardiogram, absence of other evident etiological factors, gross deficiency of diet for three months or more, improvement and reduction of heart size after specific treatment, or autopsy findings consistent with beriberi. By these criteria a great many more cases will be recognized. The omission from the diagnostic criteria of the three "traditional signs" of prominent right heart, "pistol shot" sounds, and acceleration of the circulation is a long step forward. The additional requirement of corroborative signs of nutritive failure (peripheral neuritis or pellagra) is significant.

It may well be that the criteria of Aalsmeer and Wenckebach apply to the more advanced cases, and that those of Blankenhorn apply to an earlier state;

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it is possible that biochemical analyses in the future will enable diagnoses in the incipient state of avitaminosis, even preceding the cardiovascular phenomena. It is in that direction that we must strive.

CASE REPORT

M. E., a white woman 53 years of age, entered the hospital for the first time on March 13, 1945, with a story of insomnia for ten years which was relieved at first by drinking six to eight bottles of beer. When after five years this became ineffective, she turned to whiskey and milk for a sleeping potion. For the past five or six years she had been subsisting on five or six jiggers of whiskey in milk daily. Vegetables, meat, and cereals had been completely excluded. Three months prior to admission she had had an attack of diarrhea, without melena or pus. She remained in the hospital three days before signing her release against advice. Physical examination revealed no cyanosis, dyspnea, or edema. A lemon-yellow tint of the skin was noted. The buccal mucous membranes were pale and the tongue was smooth and atrophic. Examination of the heart revealed the heart sounds to be of fair quality, with a short, soft systolic murmur audible at the apex. The rhythm was regular, with a rate of 120 per minute. The liver extended two fingerbreadths below the costal margin. The spleen was not palpable. Rectal and vaginal examinations were negative. The blood pressure was 160/50. The temperature was normal. Urinalysis was negative. Studies of the blood revealed a hemoglobin of 28 per cent, 1.85 million red blood cells per c.mm., and 8,200 white blood cells per cubic millimeter. The total serum proteins were 5.8 Gm. per cent; the albumin was 3.5 Gm. per cent, and the globulin 2.3 Gm. per cent. The blood Wassermann test was negative. The blood sugar was 101 mg. per cent and the urea nitrogen 8 mg. per cent. The hematocrit was 16 volumes per cent. The erythrocyte sedimentation rate was elevated. Tests for occult blood in the stools were negative. A chest plate revealed cardiac enlargement to the left and moderate congestive changes of both lung fields (Fig. 1).

The patient re-entered the hospital on March 24, 1946, because of extreme weakness, shortness of breath, and swelling of the ankles, all of ten days' duration. She gave a history of having consulted a physician five years previously for weakness which had then been attributed to anemia. Since that time her teeth had been in poor condition, she had been unable to eat properly, and had subsisted on milk and alcohol with a resultant weight loss of 20 pounds. The anemic state had remained untreated.

Physical examination revealed marked dyspnea, evidences of weight loss, lemon-yellow sclerae, and marked conjunctival pallor. There were no petechiae. The tongue was pale and extremely smooth, the papillae were atrophic; fissures were present at the angles of the mouth. The neck veins were distended, but revealed normal systolic collapse. Bilateral basal moist râles were audible and the breath sounds were diminished at the right base. The cardiac apex was palpable in the fifth intercostal space beyond the midclavicular line. The rhythm was regular at a rate of 120 per minute. The palpable and audible phenomena of gallop rhythm were noted to the left of the sternum. There was a soft systolic murmur over the precordium. The second aortic and second pulmonic sounds were of equal intensity. Abdominal palpation revealed hepatic enlargement to the umbilicus; the spleen was palpable one fingerbreadth below the costal margin. Marked sacral and pretibial edema were evident. The deep reflexes were normal and position sense was intact. There was neuritic tenderness in both calves.

A summary of the laboratory data is given. The blood studies are shown in Table I, and the bone marrow studies in Table II. The hematological interpretation was that the marrow findings of April 8, 1946, were consistent with hyperchromic macrocytic anemia; on May 8, 1946, the findings were comparatively normal. Nutritional defects with deficiency of the extrinsic factor of Castle may have been causative.

On March 26, 1946, the total proteins were 6.0 Gm. per 100 c.c.; the albumin was 3.5 Gm. and the globulin 2.5 grams. The blood cholesterol was 126 mg. per cent and the cholesterol esters 62 mg. per cent. The blood glucose was 115 mg. per cent and the urea nitrogen 15 mg. per cent. The icterus index was 5 units and the thymol turbidity test of Maglagen was 7 units

TABLE I. HEMATOLOGIC FINDINGS

DATE	HEMATOCRIT (PER CENT)	Hb (PER CENT)	R.B.C. IN MILLIONS	W.B.C.	POLYS.		DIFFERENTIAL STUDY		EOS.	BASO.	RETICULOCYTES (PER CENT)
					RODS	SEGS	LYMPHOCYTES	MONOCYTES			
3/24/46		23	1.02								
3/25		20	1.00	8,000	4	58	30	2	4	2	
3/27					6	76	16	2			0.3
4/10	30 vol										
4/11		60	3.07	5,000	2	66	30	2			
4/13											0.4
4/15		55	2.83	5,000	2	54	44				0.4
4/22		70	3.6			54	36	8	2		
4/27											0.6
4/29		67	3.45	5,800	2	38	44		14	2	
5/2		62	3.12	7,200	6	78	14	2			0.8
5/6		76	3.92	6,000	2	62	26				
5/9	26 vol										
5/13		72	3.4	6,400	2	50	40	8			
7/10		80	4.1	7,300	2	52	39	7			

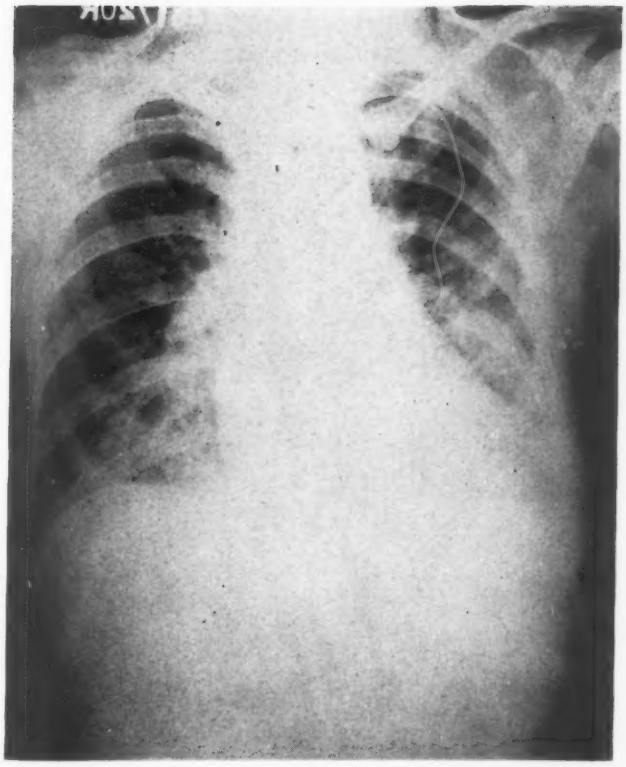


Fig. 1.—March 15, 1945. Teleroentgenogram showing moderate cardiac enlargement and pulmonary congestion.

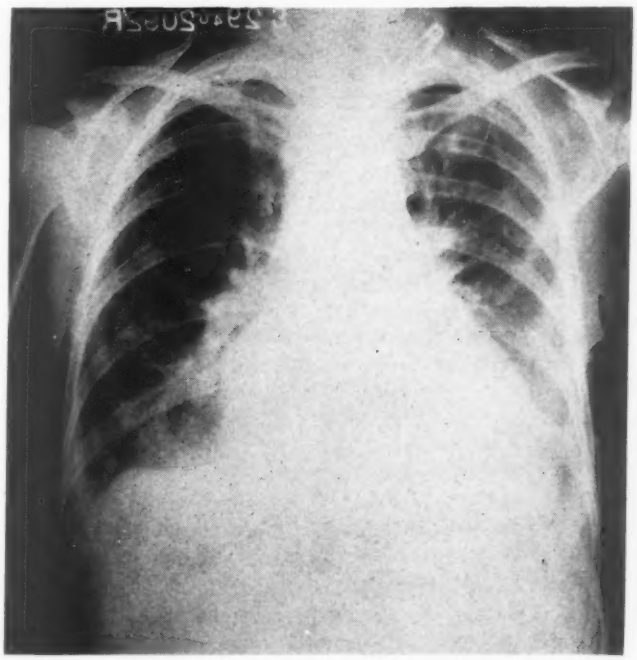


Fig. 2.—March 29, 1946. Teleroentgenogram showing marked cardiac enlargement and pulmonary congestion prior to sufficient specific therapy.

TABLE II.

	ON 4/8/46 (PER CENT)	ON 5/8/46 (PER CENT)
Myeloblasts	4	2
Myelocytes	8	19
Meta myelocytes	21	44
Polymorphonuclear leucocytes	23	14
Megaloblasts	11	0
Normoblasts	33	9
Erythroblasts	0	12

(normal to 4). The alkaline phosphatase was 3.3 Bodansky units. The prothrombin time was 6 minutes (Howell). The blood Wassermann test was negative. Hemolysis of the erythrocytes began at 0.46 per cent, and was complete at 0.36 per cent. The galactose tolerance test was normal. Urinalysis, including the test for Bence-Jones protein, was negative. Examination of the stools for occult blood was negative.

Gastric analysis with histamine revealed no free hydrochloric acid; the total acidity was 8.0, 13.4, 10.0, 13.4, and 11.0 in the fasting specimen, at 15 minutes, 30 minutes, 45 minutes, and one hour, respectively.

Roentgen-ray studies revealed calcification of the arteries of the legs, forearms, and pelvis. There was nonspecific rarefaction of the bones of the legs and osteoporosis of the left humerus. The skull was negative. Flat plate of the abdomen and detailed gastrointestinal studies revealed no abnormalities. On March 29, 1946, chest films revealed the heart to be enlarged in all diameters; there was bilateral pulmonary congestion and a small amount of fluid at both costophrenic angles (Fig. 2).

The rectal temperature was 100.5°F. during the first three days and then remained normal. The blood pressure readings were 140/50 (on admission) and then 114/62, 120/62, 124/66, 140/86, and 136/80. The weight increased from 87 to 89 pounds.

An electrocardiogram made on March 27, 1946, showed a P-R interval of 0.16 second, QRS duration of 0.08 second, and a heart rate of 108 per minute. All complexes were of low voltage. T_1 was isoelectric; T_2 and T_3 were positive but of low voltage (Fig. 3,*A*). On April 25, 1946, (Fig. 3,*B*) the tracing was normal. The T waves were upright in all leads, the P-R interval was 0.18 second and the QRS duration was 0.06 second.

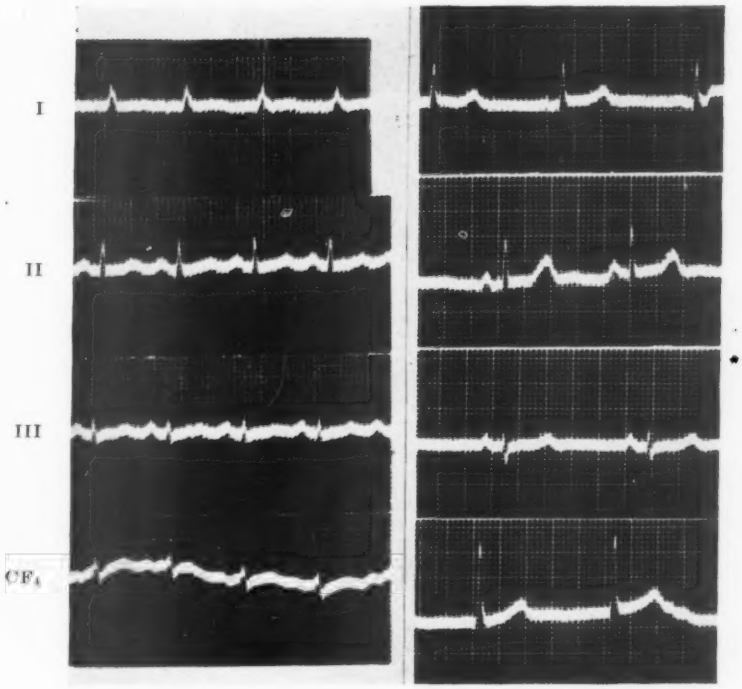
On April 8, 1946, the venous pressure was 15 cm. of water and the arm-to-tongue circulation time (decholin), 12 seconds. On April 29, 1946, the venous pressure was 10 cm. of water and the arm-to-tongue time, 8 seconds.

On the following therapy, improvement was rapid so that by April 8, 1946, evidences of congestive failure had subsided in great part. Cervical vein distention was no longer present and only slight sacral edema persisted. By May 25, 1946, neither the liver nor spleen was palpable, no edema was present, and the patient was then discharged, greatly improved.

Therapy consisted of the daily oral administration of thiamine chloride, 100 mg., niacin, 150 mg., vitamin C, 200 mg., and vitamin A and D concentrate tablets. Blood transfusions of 500 c.c. were given on March 25, March 30, and April 9, 1946. A full diet was given as soon as it could be tolerated. Liver extract parenterally was not begun until April 10, 1946 by which time all signs of failure had disappeared.

On July 10, 1946, six weeks after discharge, the patient's weight had increased from 89 to 106 pounds. She had been on a full balanced diet with vitamin supplements. All alcoholic beverages were interdicted. Her functional capacity was excellent (she could walk two miles) and she was symptom-free.

Physical examination revealed no residual signs of vitamin deficiency. There was no dyspnea, cyanosis, edema, or venous congestion. The liver and spleen were not palpable. The heart



A. *B.*

Fig. 3.—*A*, March 27, 1946. Electrocardiogram revealing low voltage of QRS complexes and flattening of the T waves before specific therapy. *B*, April 26, 1946. Normal electrocardiogram following specific therapy.

rate was 84 per minute and there was a regular sinus rhythm. A soft systolic murmur was audible over the precordium.

Electrocardiographic study revealed no significant changes in the comparable leads (Fig. 4). A teleroentgenogram revealed that the heart size still remained small and that there was no pulmonary congestion (Fig. 5).

It should be noted that on the first admission with severe anemia and minimal signs of failure, the heart size (Fig. 1) was not so great as on the readmission with the same degree of anemia and severe congestive failure (Fig. 2). Follow-up study (Fig. 5) revealed striking decrease in the heart size.

COMMENT

This case presents many of the outstanding features of cardiovascular manifestations of thiamine deficiency. It is interesting that the severe anemia, as well as signs of avitaminosis, were present on the first admission without signs of frank congestive heart failure. Yet on the second admission the patient was in advanced congestive failure with very little advance in her anemia. The role of anemia in congestive heart failure is well known;[10] the pathologic physiology of the circulation has been amply studied,[11] and roentgenographic changes of the heart in anemia have been described[12,13] with reversal of the heart size

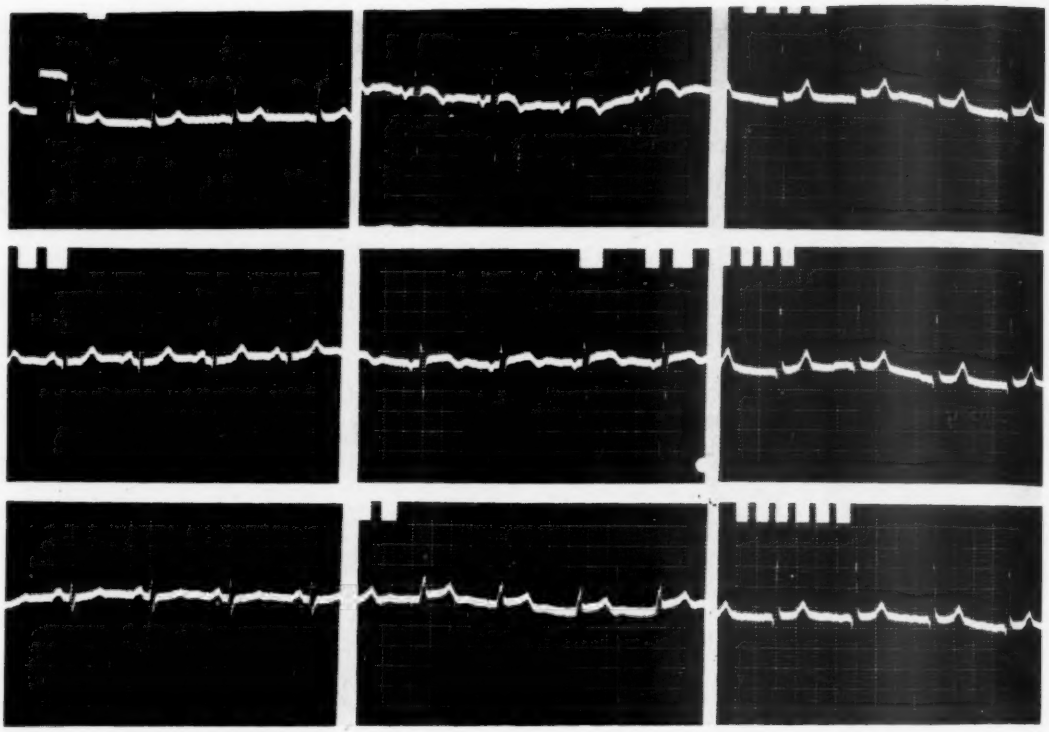


Fig. 4.—July 10, 1946. Follow-up electrocardiogram remains within normal limits six and one-half weeks after discharge from hospital.

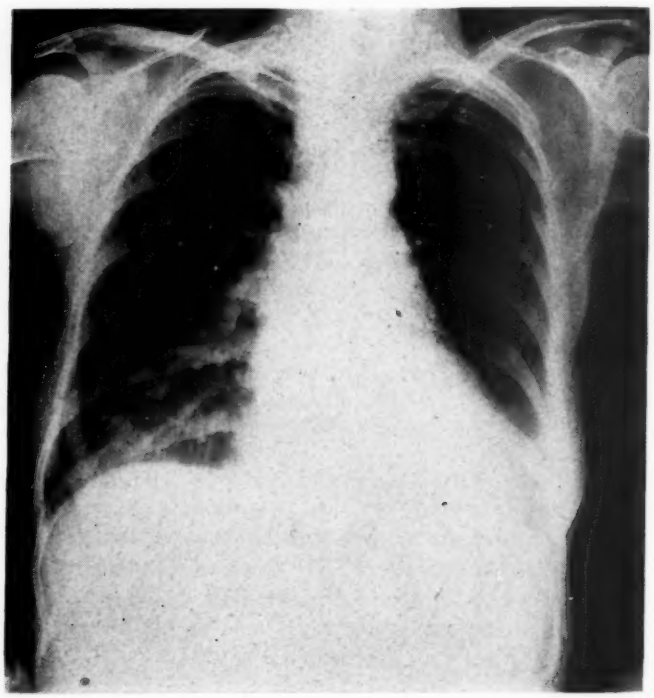


Fig. 5.—July 10, 1946. Follow-up teleroentgenogram reveals smaller heart size and absence of pulmonary congestion six and one-half weeks after discharge from hospital.

after correction of the anemia. The varied effects of acute anemia (hemorrhage, etc.) versus chronic anemia on the cardiovascular mechanism need no repetition.

In our case the prolonged inadequate diet, the physical findings of dietary deficiency, the enlarged heart with sinus rhythm, the dependent edema, the elevated venous pressure with comparatively rapid circulation time, the high pulse pressure on admission, coupled with the return of the electrocardiogram to normal, the reversal of cardiac enlargement, and the disappearance of signs of failure on specific therapy all support the presence of beriberi heart disease.

Obviously the severe anemia and probably arteriosclerosis were additional factors. The rapid response to vitamin therapy, even before the hematological response, is worth noting. Digitalis and the mercurial diuretics were not exhibited. The subsequent well-being of the patient with good functional capacity on a satisfactory dietary regime with vitamin supplements is significant.

It is well to point out the importance of precipitating causes such as infection and exertion superimposed on pre-existing vitamin deficiencies[14] which might by themselves be insufficient to cause cardiac symptoms. The rectal temperature of 100.5° F. in our case does not necessarily suggest infection; it may be attributed to congestive failure alone.[3,15a,15b,15c]

DISCUSSION

The reversible enlargement of the heart as seen in beriberi also occurs in myxedema, arteriovenous aneurysm, anemia, and following desoxycorticosterone overdose and withdrawal.[16] In the latter work[16] an attempt was made to show the basic physiologic similarities in desoxycorticosterone overdosage and thiamine deficiency.

The reversal of the electrocardiographic changes is well known in beriberi heart disease.[17,18] Prolongation of the Q-T interval occurs here as well as in hypoparathyroidism, Addison's disease, uremia, and in such conditions as rheumatic carditis and cardiac infarction.[17,18] The typical changes have been induced by diets deficient in thiamine and returned to normal on thiamine administration.[19] T waves may become temporarily inverted at the start of specific therapy with vitamin B_1 and might be mistaken for coronary disease.[3,20,21] Heart failure has recently been induced by producing experimental beriberi.[22]

Observations related to circulatory distrubances in beriberi have shown increased cardiac output, elevated venous pressure, and accelerated speed of circulation.[3,23] In the light of Blankenhorn and associates'[4,5] data, it is likely that earlier stages of deficiency will yield other data.

SUMMARY

1. The recent diagnostic advances in the cardiovascular manifestations of beriberi have been emphasized.

2. The importance of superimposed etiological factors such as anemia, infection, exertion, have been stressed.

3. A typical case of avitaminosis with associated severe anemia and cardiovascular disturbances of thiamine deficiency has been presented.

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CORONARY ARTERITIS WITH FATAL THROMBOSIS DUE TO SALMONELLA CHOLERAESUIS VARIETY KUNZENDORF

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THE subject of Salmonella infection has been comprehensively reviewed by Bornstein[1] and the following remarks are based on his report. Salmonella infections may be divided into three clinical forms; Salmonella fever, Salmonella septicemia, and Salmonella gastroenteritis. There is some overlapping with changes from one form to another. It is only possible in a general way to correlate the species of invader with the type of clinical disease. Nevertheless, it is apparent that *S. choleraesuis*‡ is a virulent pathogen in man and is more likely to cause septicemia and death than any of the other common Salmonella. In the tabulated records of 500 human Salmonella infections from the N. Y. Salmonella Center, fifty-five were caused by *S. choleraesuis;* of these fifty-five, twenty-one were instances of septicemia and nine (16 per cent) were fatal. Salmonella has been reported as a cause of endocarditis, meningitis, osteomyelitis, and abscesses in many parts of the body. There have been few specific correlations between the observed human pathology and the implicated Salmonella species. In general, the infection may be associated with no lesions, with typhoidlike lesions, or with lesions similar to those produced by the pyogenic cocci. When no lesions are present, death is attributed to toxemia. In the experimental lesions produced in the mouse by intra-abdominal injections of *S. typhimurium*, either living organisms or antigenic extracts, there are found mononuclear infiltrations of the adrenal medulla with parenchymal degeneration, focal necroses in the liver, follicles of the spleen and lymph nodes, and congestion of the portal vessels with or without thrombosis and hemorrhage. The latter lesions may have some bearing on the case to be presented.

Salmonella choleraesuis is more sensitive to the sulfonamides, particularly sulfaguanidine, than most other Salmonella organisms. Administration of sulfonamides in disease caused by this species is recommended.

CASE REPORT

W. Q. A., a 48-year-old white man, was admitted to this hospital on March 24, 1945, complaining of a discharge from the right ear which had begun fourteen days previously, one week after a cold. He had been given twenty-four tablets of a sulfonamide preparation. During the

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‡This organism is referred to in the older literature as *S. suipestifer*. The variety Kunzendorf is the so-called "European" strain, differing from the "American" strain in hydrogen sulphide production and certain other cultural reactions.

administration of this drug he noticed pain in the legs and right arm with slight swelling of the right wrist. Three to four days before admission he noted chills and fever. The history otherwise was irrelevant.

Physical examination on admission revealed a thin man who did not appear acutely ill. The temperature was 100° F., and the pulse rate 100 per minute. The right ear drum was perforated and there was a purulent discharge in the external auditory canal. There was slight tenderness over the tip of the right mastoid but no swelling. The throat was congested. The blood pressure was 130/80. The heart and lungs appeared normal. There was no splenomegaly, lymphadenopathy, skin rash, or petechiae. Neurological examination was entirely negative. There was tenderness of both calves and the right wrist with no obvious swelling. The white blood count was 11,600, the differential count was normal, the red blood count was 4.25 million, and hemoglobin was 86 per cent (13.9 grams, photoelectric). The blood serology was negative. The urine was normal. The diagnosis on admission was acute purulent otitis media with probable mastoiditis.

An x-ray film of the mastoid sinuses was negative. The ear continued to drain moderately, but the patient had no pain. The consulting otologist did not believe that a mastoiditis was present. Sulfadiazine therapy was instituted on March 26, and on March 27 the blood level was 4.4 mg. per 100 cubic centimeters. The drug, however, was discontinued after only 3 Gm. were taken because of its possible etiological role in the production of the arthralgia. At this time the presence of acute rheumatic fever was considered likely and the patient was given salicylate therapy, receiving 1,080 grains by rectum in six days. The temperature ranged between 100 and 103.8° Fahrenheit. An x-ray film of the chest was negative. On April 1, a small macular hemorrhage was seen in the right ocular fundus. It was associated with blindness of this eye, which persisted until death. On April 2, a purpuric spot appeared on the left palm. It was believed then that the patient was exhibiting a late reaction to the sulfonamides, manifested by arthralgia, fever (which reached 106° F. on April 4), and a probable thrombocytopenia. The platelet count, however, was 550,000, and the white cell count reached 19,600, with 86 per cent polymorphonuclear leucocytes. Salicylates were discontinued on April 1. On April 3, another hemorrhage was seen in the right fundus and paresis of the right upper extremity occurred. The neck remained supple. A mitral systolic murmur was heard on this date and the possibility of septicemia or brain abscess was considered. Spinal tap revealed an initial pressure of 150 mm. of water, a clear fluid, and normal manometrics. A cell count and the protein and dextrose content of the fluid were normal.

A blood culture was made on April 3, and reported as negative. The patient was given penicillin therapy, however, because of his critical febrile condition despite the fact that no organisms had as yet been isolated. Purpuric eruptions now appeared on both palms. The spleen was not palpable. There were no petechiae. The neurological findings remained unchanged. It was felt that the apical systolic murmur was of no diagnostic significance. The patient remained alert mentally. On April 5, the right pupil was found to be fixed while the left reacted sluggishly. On this date the blood culture of April 3 was reported positive for an unidentified gram-negative rod. The urine culture was positive for the same organism. The Widal and Brucella agglutination tests were negative. The intradermal skin tests for brucellosis were also negative.

A culture was sent to the University of Kentucky Agricultural Experimental Station and was later reported by Dr. Phillip Edwards as *Salmonella choleraesuis*, variety Kunzendorf. In the interim, in vitro studies with reference to penicillin sensitivity of the organism revealed that it grew luxuriously in a medium containing 25 units of penicillin per cubic centimeter. With this information at hand, and because no apparent improvement had followed administration of the drug, penicillin therapy was discontinued after the patient had received 1,620,000 units. The paresis of the right arm improved and soon disappeared but the right eye remained blind.

Endocarditis due to Salmonella appeared to be the most likely diagnosis at this time. The patient continued to have fever, although at a lower level. The apical systolic murmur remained unchanged and there was some improvement in the general condition. At 8:30 A.M., on April 24 the patient was found to be in shock with marked venous congestion of the neck and head. The heart sounds were poor. The blood pressure could not be recorded. An electrocardiogram

revealed an acute anterior wall infarction (Fig. 1). A gallop rhythm was present and Cheyne-Stokes respirations soon ensued. The patient expired at 3:35 P.M. the same day.

The final clinical diagnoses were:

1. Sepsis, due to *Salmonella choleraesuis*, variety Kunzendorf.
2. Heart disease of unknown etiology, probably bacterial embolization, with coronary occlusion and myocardial infarction.
3. Embolic closure, right retinal vessels and possibly the left lenticulostriate artery, with right hemiparesis.

Autopsy.—The heart weighed 350 grams. The valves and chambers were normal. The coronary arteries were thin-walled and widely patent, except for a gray, soft, slightly adherent occlusive thrombus in the left anterior descending artery about 2 cm. from the aortic ostium, measuring about 1 cm. in length. The myocardium of the anterior wall of the left ventricle was mottled dark red and yellow, contrasting with the red-brown normal muscle elsewhere.

The spleen weighed 350 grams. It was soft and red, with prominent corpuscles. There was an abscess at the lower pole containing about 10 c.c. of thick yellow pus from which *S. choleraesuis* organisms were cultured.

The colon exhibited mucosal hemorrhages in its ascending portion for a distance of about 15 cm. above the cecum.

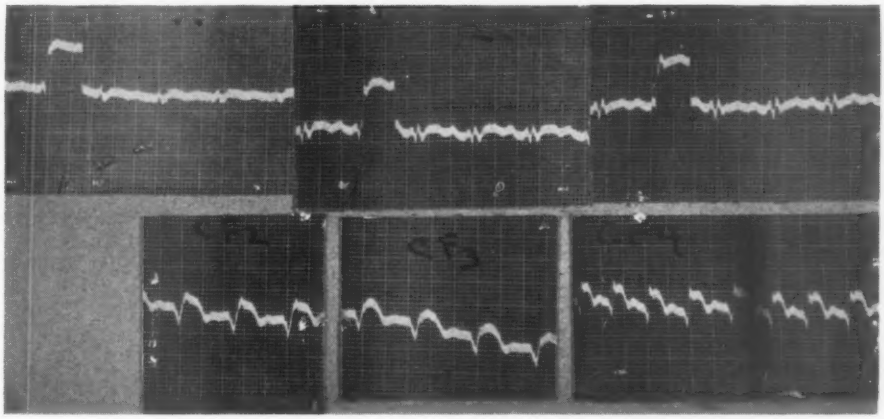

Fig. 1.—Electrocardiogram of April 4, 1945, showing an acute anterior wall infarction.

The brain was normal grossly. It was symmetrical. The arteries of the circle of Willis were the seat of moderate arteriosclerosis but no closure was found. Multiple sections were made at frequent intervals through all parts of the brain. No grossly visible abnormalities were found in the cerebrum, midbrain, pons, medulla, cerebellum, or upper cervical cord.

The other organs were not abnormal grossly.

Microscopic.—

Heart: One section was taken through the anterior wall of the left ventricle, passing through the occluded coronary artery (Fig. 2). The lumen of the artery contained laminated fibrin peripherally and fresh blood centrally. The endothelial cells were absent. The remainder of the intima was disorganized, vascularized, and infiltrated with small round cells and a few polymorphonuclears. The media was similarly disorganized, thinned, and infiltrated with inflammatory cells. The elastic tissue was fragmented and destroyed at many points. The adventitia was heavily infiltrated and thickened. At some points the cellular exudate consisted exclusively

of polymorphonuclears and was associated with necrotic cells and pyknotic nuclei. Gram stain revealed rare gram-negative rodlike structures which were not unequivocally bacteria. This inflammatory reaction extended into the surrounding epicardial fat. Elsewhere in the epicardium were scattered small round cells. The underlying myocardium at this point contained an interstitial exudate, chiefly of polymorphonuclear cells. The myocardial fibers, however, were only slightly degenerated and in the region of the most marked interstitial inflammation were essentially normal. A medium sized artery in the section showed fibrinoid necrosis of parts of the media without any inflammatory reaction. Another section was taken through the myocardium of the left ventricle laterally. The picture here showed extensive myocardial damage, ranging from acute swelling, edema, and necrosis of muscle fibers to a small round cell and polymorphonuclear infiltration of necrotic muscle and, finally, to vascular granulation tissue replacing the muscle. No large vessels were included in this section.

Fig. 2.

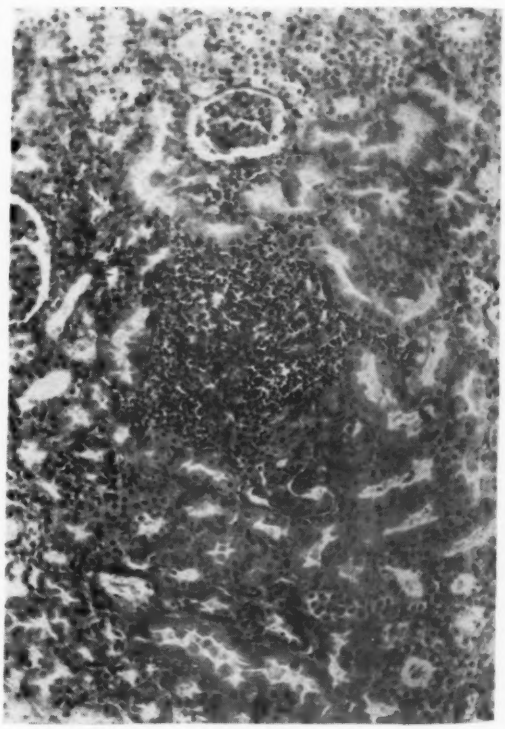

Fig. 3.

Fig. 2.—Section of left anterior descending coronary artery. The edge of the thrombus is above. Note the extensive polymorphonuclear exudate in the outer portion of the media and adventitia. Hematoxylin and eosin stain: x400.

Fig. 3.—Section of the kidney. In the center is a glomerulus which is disorganized, and collected both in and around it are polymorphonuclear cells. Hematoxylin and eosin: x400.

Liver: The general architecture was well preserved. There was a slight central atrophy of the lobules. There was marked fatty infiltration and degeneration of the liver cells which was focal and not limited to any part of the lobule. Rare arteriolar lesions consisting of thickening of the walls by polymorphonuclear leucocytes were found.

Spleen: The corpuscles were well preserved. The pulp was moderately congested. There was a considerable proliferation of plasma cells and histiocytes in the cords of Billroth. The arteries were thick-walled, with considerable proliferation and swelling of the endothelial cells. The section passed through the abscess noted grossly. The abscess was lined by fibrin and granulation tissue. Between this and the normal parenchyma was a thick zone of organizing hemorrhage. There were some areas of necrosis but little inflammatory response.

Kidneys: (Fig. 3.) The general architecture was intact. There were striking focal inflammatory lesions whose unit was the glomerulus and the surrounding tissue. These lesions consisted of marked round cell infiltration, at first near the hilus of the glomerulus, and later spreading around the glomerulus on all sides. In the glomerulus changes ranged from closure of the proximal capillary loops to necrosis of the entire structure. It was difficult to distinguish the afferent arteriole in these areas but it was apparently swollen and even occluded. Occasionally, a larger renal artery was involved, with destruction of the wall and marked granulomatous reaction. Except for these changes described the renal vessels were not unusual.

Gastrointestinal Tract: A section was taken through the hemorrhagic zone in the cecum. There was a superficial necrosis of the mucosa. The veins were markedly distended with blood. No inflammatory changes were found.

Bacteriology: From the splenic abscess there was isolated the same organism which had been present in the blood stream during life, *Salmonella choleraesuis*, variety Kunzendorf.

Diagnoses: 1. Septicemia, due to *Salmonella choleraesuis*, variety Kunzendorf.

(a) Coronary arteritis, with thrombosis
(b) Myocardial infarction, recent
(c) Acute myocarditis
(d) Focal embolic glomerulonephritis
(e) Cloudy swelling and fatty degeneration of the liver
(f) Splenic abscess

2. Cerebral arteriosclerosis.

COMMENT

An outline of the clinical course in this case has been presented. The upper respiratory infection and right otitis media started three weeks before admission, and ended one week after admission at a time when the fever and chills of the Salmonella infection were at their peak. It is apparent, in retrospect, that the first illness was not part of the second. The second illness began with fever, chills, and joint pains within a few days of admission. The temperature chart (noting the antipyretic effects of large doses of salicylates exhibited from March 27 to April 1) is obviously that of continuous fever. In view of the isolation of the *S. choleraesuis* organism whenever sought for in the blood stream from April 3 to April 24, it seems certain that this entire latter illness was a Salmonella infection.

The role played by sulfonamides is, of course, debatable. The patient certainly never received enough of the drug for adequate therapeutic effect against the Salmonella infection. The dose of 12 Gm. administered in the period before admission is very little to account for a febrile reaction. Furthermore, the normal formed elements of the blood, normal urine, and absence of skin eruption are evidence against any clinical role having been played by these drugs. Though the pathologic lesions somewhat resemble those ascribed by

Rich[2-4] to sulfonamide reactions, they differ in the marked polymorphonuclear reactions and the picture of purulent thromboarteritis seen in our case. Also, there is the lack of focal liver necroses which we have come to associate so commonly with sulfonamide toxicity. The splenic abscess and positive cultures at autopsy, on the other hand, strongly favor a diagnosis of Salmonella etiology.

Periarteritis nodosa was also considered. Evidence against this diagnosis is the absence of eosinophilia in the blood or tissues, the finding of a causative organism, and the distribution and type of the lesions. The slides of the coronary artery, kidneys, and liver in our case were reviewed by Dr. Paul Klemperer, who feels that this is a true arteritis. Dr. Klemperer has seen other instances of infectious vasculitis due to Salmonella organisms.

SUMMARY AND CONCLUSIONS

A case of *Salmonella choleraesuis* septicemia is presented in which death was due to thromboarteritis of a coronary artery. The renal vessels were extensively involved in a similar process, and the hepatic vessels to a lesser degree. This particular type of specific lesion has not, to our knowledge, been previously described.

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MASSIVE HYDROPERICARDIUM WITH COMPRESSION AND ANGULATION OF THE INFERIOR VENA CAVA

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THE effect of varying degrees of hydropericardium on the large venous trunks entering the right auricle of the heart is very accurately illustrated by the following case.

CASE REPORT

A 26-year-old Negro woman was admitted to the Lincoln Hospital on Jan. 1, 1940, because of swelling of the abdomen and dyspnea on exertion. The family history was irrelevant. The past history included the fact that the patient had been a heavy drinker. At the age of 3 years she had been observed in an institution because of a "swelling in the neck." She gave an indefinite history of syphilis. There was no history of a rheumatic infection. The present illness began a year and a half before admission, at which time the patient was hospitalized for seven weeks at another institution because of dyspnea and swelling of the abdomen and lower extremities. Physical examination at that time revealed a hydropericardium and enlargement of the liver. On x-ray examination the lung fields were clear. An electrocardiogram showed auricular fibrillation, ventricular extrasystoles, and low voltage. Several pericardial taps were done and the patient was discharged in an improved condition. The clinical diagnoses were: acute rheumatic heart disease, auricular fibrillation, and pericardial effusion.

On admission to Lincoln Hospital, the temperature was 101° F.; the pulse rate, 100; and the respiratory rate, 24 per minute. The pulse was completely irregular. The blood pressure was 105/60. There was marked edema of the abdominal wall and of the lower extremities. The neck veins were distended and there was slight exophthalmos. The heart was markedly enlarged and the lungs were congested. A short systolic murmur was audible over the precordium. The abdomen was enormously distended by fluid. The liver reached to the umbilious.

Examination of the blood showed hemoglobin of 90 per cent, 5,000,000 erythrocytes, 7,000 white blood cells, and a normal differential count. Blood Wassermann and Kahn reactions were negative. Urinalysis showed a specific gravity of 1.010, a two-plus albuminuria, and no sugar. Bromsulfalein test revealed that 100 per cent of the dye was present in the blood in five minutes and 75 per cent in thirty minutes. Total proteins were 9.37 Gm. per 100 c.c.; urea nitrogen, 11 to 16 mg.; blood sugar, 81 mg.; cholesterol, 150 mg.; and icteric index, 12.5. A Mantoux test was positive at a dilution of 1:10,000.

Two determinations of the circulation time with 0.5 c.c. of paraldehyde were made. The drug was detected within 50 and 35 seconds, respectively.[4] Two determinations of the cubital venous pressure showed pressures of 31.5 cm. and 29.5 cm. of water, respectively. The electrocardiogram revealed auricular fibrillation, ventricular premature beats from multiple foci, extremely low QRS voltage, and flattened T deflections. An x-ray film of the thorax revealed the pericardium to be distended with fluid and so sharply delineated as to simulate marked elevation

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of diaphragmatic domes (Fig. 1). An abdominal paracentesis was done on January 16, and 4 liters of clear amber-colored fluid were withdrawn; the fluid showed a 4-plus protein reaction and contained 170 leucocytes per cubic millimeter. The liver was then found to be markedly tender and to extend to the umbilicus. A second x-ray film on January 19 revealed no change in the thoracic outline. On February 13, 2,400 c.c. of greenish-yellow fluid was removed from the pericardial sac and half the volume replaced with air[5,9] (Fig. 2). The patient was discharged April 14, 1940, somewhat improved.

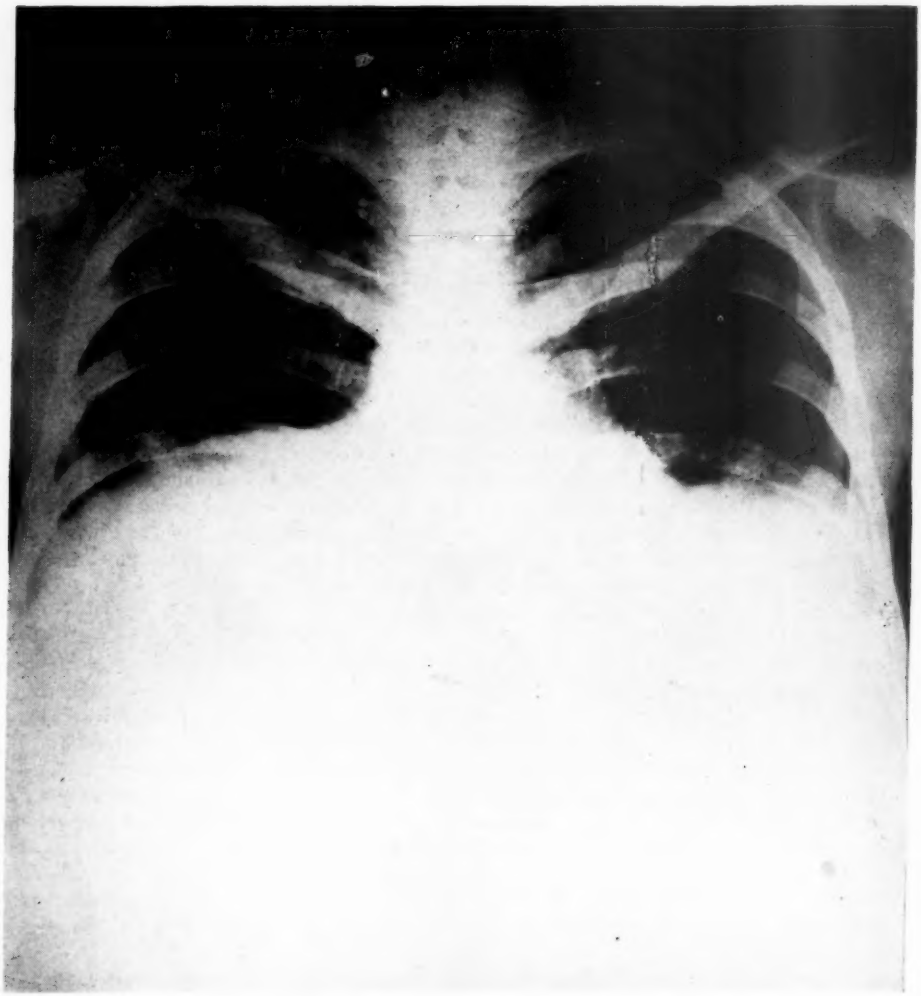

Fig. 1.—Jan. 9, 1940. Upright posteroanterior view of the chest. Extreme hydropericardium. Lateral borders of the pericardial sac are sharply demarcated.

After having remained at home for two months, the patient was admitted to the Presbyterian Hospital on Oct. 10, 1940. She was markedly cyanotic, dyspneic, and orthopneic, with an enormous abdomen on whose surface fine striae could be made out. Pitting edema extended up to the level of the scapular angles and involved the lower chest and abdominal wall. There was marked distention of the neck veins which did not pulsate and there was no edema of the upper

extremities. All accessory muscles were being used in respiration and the thorax seemed to move well. At both lung apices, breath sounds and moist râles were audible; at the lung bases, breath sounds were distant and there was diminution in resonance with absence of fremitus. No cardiac apex impulse or diastolic shock was felt. The borders of the heart were difficult to outline on percussion since the lower chest on both sides showed diminished resonance. However, there was an area of increased dullness which extended 7 cm. to the left and 6 cm. to the right of the midsternal line in the fifth intercostal space. Heart sounds were distant and of poor quality. The heart rate was extremely rapid and no murmurs were heard. The abdomen was hugely distended, tense, and nontender; a definite fluid wave was felt. No dilated veins were visible in the skin of the abdomen. After the removal of 14 liters of fluid by paracentesis, a firm, slightly tender, rounded liver edge could be made out about 7 cm. below the costal margin in the right midclavicular line. The spleen was not felt. There was no clubbing of the fingers. The tem-

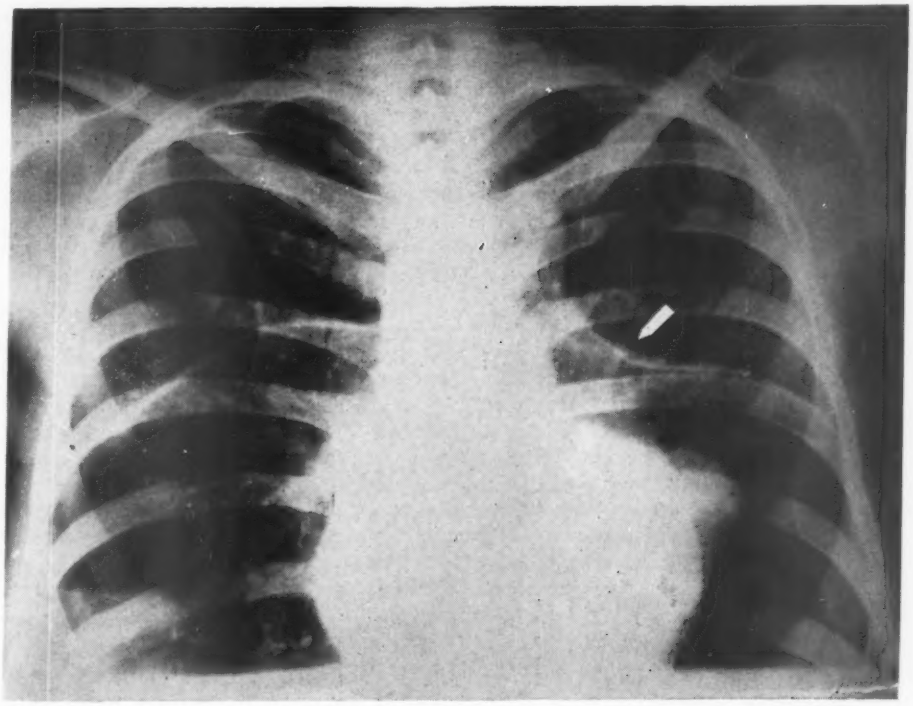

Fig. 2.—Feb. 13, 1940. Upright posteroanterior view of the chest. After removal of 2,400 c.c. of fluid from the pericardial sac and the injection of 1,760 c.c. of air, a hydropneumopericardium resulted. Note the thickened, greatly stretched parietal pericardium (arrow), and the large bulge to the right of the heart shadow (traction upon wall of right auricle).

perature was 98.8° F., the heart rate was 190 (the pulse could not be felt), and the respiratory rate was 44 per minute. The blood pressure was not obtainable. The sedimentation rate was 5 mm. in one hour. The Kline test was negative, blood nonprotein nitrogen was 42 mg. per 100 c.c., and blood sugar was 83 milligrams. A right thoracentesis yielded 600 c.c. of fluid which showed a specific gravity of 1.008 and 1,160 lymphocytes per cubic millimeter. The abdominal fluid showed a specific gravity of 1.015 and 440 lymphocytes per cubic millimeter. Guinea pigs injected with ascitic and pleural fluid remained well and showed no pathologic lesions at autopsy two months after injection.

The patient was so desperately ill that only a very brief physical examination was made. It was thought that the findings were consistent with a constrictive pericarditis with obstruction to the venous return, hydrothorax, and ascites.[11] After the conclusion of the paracentesis and thoracocentesis, the patient complained of marked fatigue, but said that her breathing was much improved and that she felt much stronger. She was placed in an oxygen tent and promptly fell asleep. A little more than two hours later, without much change in the clinical picture, she suddenly expired.

Autopsy.—The examination was performed six hours after death. On gross examination the abdomen was hugely distended and the skin showed many striae. The edema of the trunk, stopped rather abruptly at the level of the shoulder blades. In comparison to the markedly edematous lower extremities, the arms appeared disproportionately small. There was no clubbing of the fingers and toes, but the nailbeds were cyanotic.

The peritoneal cavity contained 750 c.c. of clear light fluid. The peritoneum was greatly thickened and its vascular pattern was quite prominent. The liver extended 14 cm. below the xiphoid and 9 cm. below the costal margin. The dome of the diaphragm was situated at the level of the sixth intercostal space on the right and the seventh intercostal space on the left side.

The thoracic cavity contained no free fluid in the pleural spaces. The lower portion of the thorax was taken up by a tremendously enlarged pericardial sac which was tightly filled with 3,000 c.c. of slightly cloudy, greenish-yellow fluid. The lungs were pushed up and their bases were at the level of the second intercostal space. On opening the pericardial sac, the heart was found to be pushed upward, and was represented by a round knob projecting into the pericardial space. The parietal pericardium was thickened and showed several large, yellowish plaques, varying in size from 1 to about 5 cm. in diameter, especially on the anterior, posterior, and diaphragmatic surfaces. Over these plaques the surface was irregularly granular. In several places the consistency of the membrane was cartilage-like, and masses of calcification were also felt. The remaining portion of the parietal pericardium was smooth and there were no adhesions between the epicardium and the pericardium. On inspection, in situ, a heavy fold of thickened pericardium covering the inferior vena cava could be seen to compress the lumen of this vein anteriorly and laterally at the level of the diaphragm; the same fold partly obstructed the lumina of the hepatic veins at the point where they emerge from the liver (Fig. 5). The weight of the heart and the attached pericardium was 600 grams. The heart was small and round, and its external markings were obliterated. The apex was rounded. The epicardium was greatly thickened, white in color, and opaque. Its surface was irregular, and contained many hyaline plaques and areas of calcification. The auricular appendages were small, rounded, and embedded in thickened epicardium. The thickening of the epicardium extended up to the trunks of the great vessels where it quite abruptly changed to a more normal membrane. The subepicardial fat tissue was normal in amount and was orange-yellow in color. The right auricle was pulled toward the right side by the inferior vena cava which could be seen and felt as a chord stretching across the right posterior pericardium. The cavity of the right auricle was greatly enlarged, but the wall was thin; its lumen was in broad communication with the inferior vena cava. The mouth of the superior vena cava appeared normal. The foramen ovale was closed and the coronary sinus was guarded by a curtain of Chiari. The auricular appendage was empty. The tricuspid valve was normal but the ostium was much too large for the valve, thereby producing a relative insufficiency. The right ventricle was small and appeared like an appendix to the auricle. It was otherwise normal. The pulmonary valve was delicate and competent and the pulmonary aorta was normal. The cavities of the left side of the heart were normal, as were the mitral and aortic valves. There were no signs of active or healed rheumatic endocarditis. The coronary arteries were normal. The myocardium was dark brown in color and there was no scarring. The lumen of the inferior vena cava at the level of its mouth measured 3.5 cm. in diameter. Sharp angulation of the vein at the point where it entered the pericardium severely compromised the lumen. Several white plaques were present in its intima just above the diaphragm. The superior vena cava was normal in caliber and appearance. The measurements of the cardiac ostia and walls were: tricuspid valve, 15.0 cm.; pulmonary valve, 5.5 cm.; mitral valve, 7.5 cm.; aortic valve, 5.5 cm.; left ventricle, 1.0 cm.; and right ventricle, 0.12 to .13 centimeter.

The lungs weighed 300 grams each. The pleura of the left lower lobe was moderately thickened and there was atelectasis of this lobe. Otherwise, both organs were normal. The bronchial and tracheal lymph nodes were small and not remarkable. There were no apical scars or any other signs of healed tuberculosis.

The spleen weighed 250 grams. Its capsule was thickened and a few irregular plaques resembling icing were present. On cross section the pulp was congested. The liver weighed 1,380 grams. Its capsule was irregularly thickened by whitish, opaque plaques; the surface of the capsule was irregularly granular. The liver tissue was firm in consistency. On cross section there was marked congestion and distention of the lobular portions. Opaque white tissue was seen in many of the lobules about the efferent vein, sometimes extending to the portal canals. The lumina of the hepatic veins were distended and their intima showed occasional yellowish-white plaques. A few well-circumscribed, yellowish-brown adenomas were present. The largest measured about 1 cm. in diameter. The gall bladder and bile passages were normal. No gross pathologic changes were seen in the pancreas, adrenals, or pelvic organs. The kidneys were congested. The mucosa of the gastrointestinal tract was markedly congested. The neck organs were normal. The brain and spinal cord were not examined. Postmortem aerobic and anaerobic cultures of the pericardial fluids showed no growth after eight days.

Microscopic Examination: In the left ventricle, the epicardium was greatly thickened by hyaline fibrous tissue in which there were areas of calcification. Areas of infiltration consisting of lymphocytes and plasma cells were present. On the borderline between epicardium and subepicardial fat tissue no tubercles were seen. The subepicardial fat tissue appeared normal and the branches of the coronary arteries seen in it showed no abnormalities. The heart muscle fibers were smaller than normal but their striations were distinct. The nuclei appeared normal and there was a moderate amount of lipochrome pigment about them. The right ventricle revealed vacuolization in the central portion of many of the myocardial fibers. The epicardium showed changes similar to those found in the left ventricle. The auricles exhibited vacular degeneration of the muscle fibers; at times the cross striations were not well seen. No Aschoff bodies were seen in any of the sections. Sections of the valves showed no significant pathologic changes. The pericardial sac was greatly thickened by hyaline fibrous tissue and infiltrations consisting of lymphocytes and plasma cells were present in it. The diaphragm showed occasional degeneration of muscle fibers. There were no tubercles. The inferior vena cava, in a section taken from the mouth of the vein, showed thickening of the intima by plaques which were composed of smooth muscle fibers and hyaline fibrous tissue. These plaques extended partly into the media. The aorta was normal. The lungs showed moderate congestion of the capillaries and occasional lymphocytic infiltrations about blood vessels and bronchi. There was sclerosis of some of the pulmonary venules. The spleen showed marked congestion. The liver was greatly congested and showed cardiac cirrhosis. Many of the portal canals seemed larger than normal and were composed of rather dense fibrous tissue, in which there was occasional slight proliferation of bile ducts. In several places the sections presented the picture of definite portal cirrhosis. The pancreas, adrenals, kidneys, pelvic organs, and the gastrointestinal tract all showed varying degrees of congestion, but no other relevant changes. The bone marrow was active and showed the usual variety of hematopoietic cells.

Anatomic Diagnoses: Chronic pericarditis with calcification, etiology unknown. Brown atrophy of the heart. Hydropericardium, with compression and augulation of the inferior vena cava. Pick's syndrome—clinical. Ascites, anasarca, and chronic passive congestion of liver, spleen, kidneys, and intestines. Cardiac cirrhosis, portal cirrhosis and adenomas of the liver. Keloids.

DISCUSSION

Massive pericardial effusions occur most frequently in rheumatic heart disease and tuberculosis of the pericardium. Smaller effusions occur less frequently in the terminal stage of congestive heart failure, pyogenic infection,

uremia, emphysema, and myxedema. Variation in amount and position of fluid within the pericardial sac may cause diverse subjective and objective signs of circulatory insufficiency. The mechanism of the circulatory disturbances attributable to variable amounts of fluid within the pericardial sac has been the subject of extensive clinical and experimental study.[1]

There are two chief types of pericardial effusion: the central (Fig. 3,*A*) and peripheral (Figs. 3,*B* and 4). In the central type, usually caused by rapidly accumulating massive effusion, the heart is primarily compressed, particularly the right auricle. The resulting circulatory congestive failure is uniform and generalized. Both venae cavae are equally dilated and congested. In the peripheral type, a small amount of fluid may seriously compress both venae cavae and hepatic veins. Visceral congestion is localized and concentrated on the radicals of the compressed veins. The dome of the right diaphragm and the diaphragmatic surface of the liver may be compressed and flattened simultaneously, constricting the lumen of the left hepatic vein which, during its terminal course, runs almost parallel to the surface of the liver. This narrowing of the ostia of the hepatic veins leads to congestion of the liver, which then rapidly increases in size and becomes painful (Figs. 3,*B* and 4). Enlargement of the liver, which is usually greater than in cases of decompensated mitral stenosis, is then followed by ascites without significant cyanosis. Compression of the supradiaphragmatic portion of the inferior vena cava affects the return of blood from all its radicals, causing congestion and edema of the lower extremities, especially in the upright position. In addition, pressure of the increasing ascites on the abdominal portion of the inferior vena cava adds to the circulatory embarrassment. The edema of the lower extremities may rapidly recede when the patient is in the horizontal position, especially if the hydropericardium is not extreme, allowing the fluid within the pericardial sac to shift, thereby relieving the pressure on the pericardial funnel and on the inferior vena cava. However, there may be residual cyanosis due to the restricted space within the pericardial sac.[2] The shift of the pericardial effusion produces static changes affecting the superior vena cava. In the early stages of hydropericardium the patient may show nocturnal facial edema and cyanosis, with rapid recession during the day when in the sitting or upright position.

Extreme hydropericardium of the central type (Fig. 3,*A*) produces persistent compression of both the inferior and superior vena cava, followed by congestion of the jugular veins and severe cyanosis with cephalad edema. Flow of blood to the lungs is thus reduced and pulmonary congestion is not observed in hydropericardium unless left ventricular failure occurs. If the left heart functions well, and if the pulmonary veins are somewhat compressed by the pericardial fluid, the lungs may appear even paler than normal. Primary right ventricular insufficiency with auricular and caval dilatation may produce similar consequences which, however, do not occur as rapidly nor to as marked an extent as those produced by the peripheral type of stasis.

In the present case, in addition to the effect of the pressure of the massive hydropericardium on the inferior vena cava and the hepatic veins, there was a

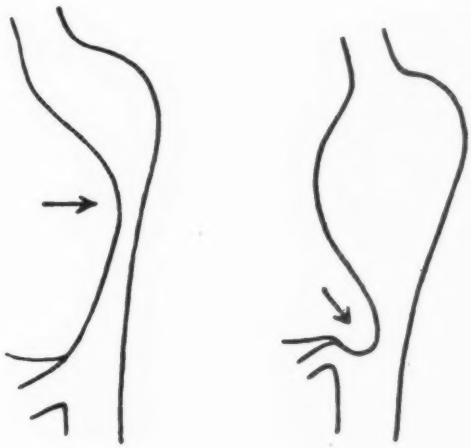

Fig. 3.—Schematic drawing (Elias and Feller) of the, *A*, central and, *B*, peripheral types of cardiac stasis caused by hydropericardium. Arrows indicate pressure points upon right auricle, inferior vena cava, and hepatic vein. The superior vena cava (above) and inferior vena cava (below). Heart tamponade, *B*, is caused by pressure of a large amount of fluid on the auricle. A smaller amount of fluid, *B*, drives a wedge into and compresses the inferior vena cava as well as the ostia of the hepatic veins, one of which is portrayed opening subdiaphragmatically into the vena cava. Note constriction of the inferior vena cava above the diaphragm and its dilatation below. Usually the left hepatic veins are more compressed than the right.

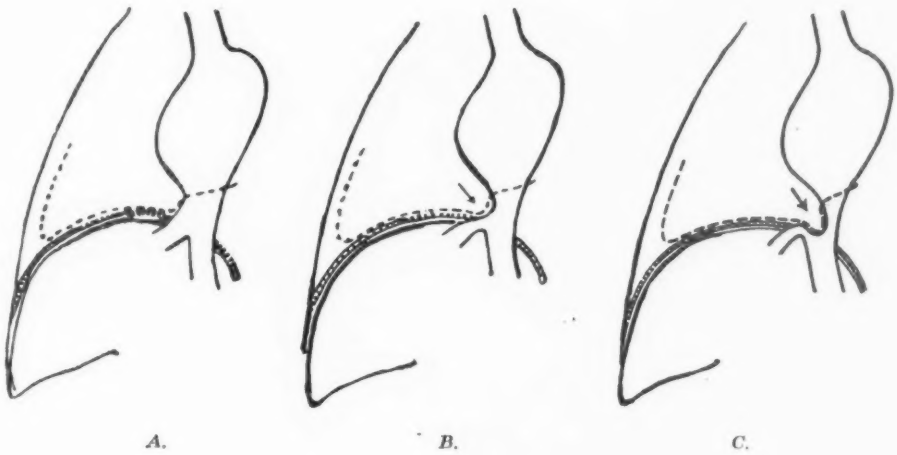

Fig. 4.—Schematic drawing (Elias and Feller) illustrating pressure effects within pericardial sac in the peripheral type of congestion. *A*, Normal relations. Superior (above) and inferior vena cava (below). The latter receives a tributary of the hepatic vein (left). *B*, Moderate effusion in exudative pericarditis. *C*, Massive effusion within the sac (experimental). At onset, a small amount of fluid collects at the base of the sac without appreciable effect. Larger amounts accumulate within the right and the dorsocaudal portion of the sac and exert pressure on the ostia of the hepatic veins prior to involvement of the inferior vena cava. Congestion of the liver precedes edema of the legs. Arrows indicate pressure points. Note angulation (pressure) of the inferior vena cava.

severe kinking of the inferior vena cava (Fig. 5) produced by a considerable traction upon the wall of the right auricle. The marked dyspnea and orthopnea, which were so extreme in this case, were related to the insufficiency of the tricuspid valve in addition to the tamponade effect of the fluid. The compression of the inferior vena cava, together with the narrowing of orifices of the hepatic veins, readily accounts for the extreme passive congestion and edema of the lower extremities, the trunk, the liver, and the ascites.

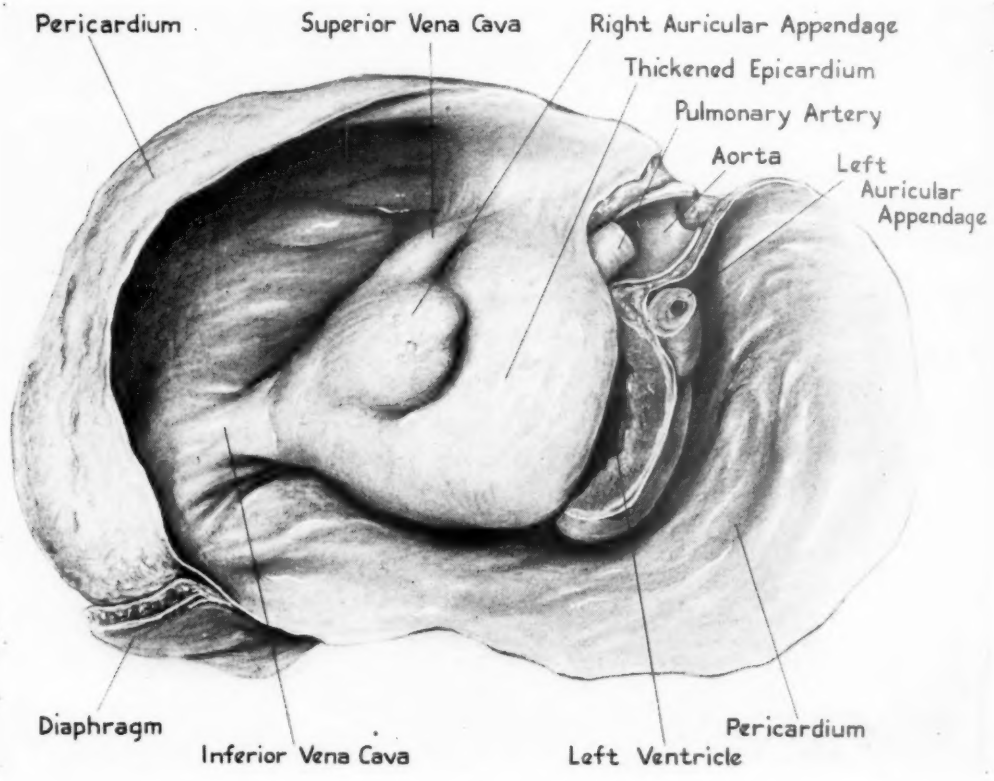

Fig. 5.—Extreme hydropericardium with angulation and compression of the inferior vena cava.

The pericardial disease in this case was obviously of a chronic nature, as evidenced by the extreme distention of the sac and marked fibrous thickening of its wall as well as by the areas of hyalinization and calcification.[6] The etiology of the pericardial disease is obscure. It is unlikely that rheumatism was the causal agent because of the absence of rheumatic changes of the valves and myocardium. Despite the history of syphilitic infection a syphilitic etiology is unlikely; the serologic reactions for syphilis were negative and no other syphilitic manifestations were found. No gross or histologic evidence of active or obsolete tuberculosis was discovered at autopsy.[10]

SUMMARY

1. A case of massive hydropericardium of obscure etiology and long duration is described.

2. Hydropneumopericardium was induced and characteristic roentgenograms were obtained.

3. The physiologic mechanisms involved are reviewed with particular emphasis on the central and peripheral types of hydropericardium. Isolated and disproportional visceral congestion and edema is explained by the latter type and differentiated from the usual congestive mechanism in decompensated heart failure. The traction upon the wall of the right auricle found at autopsy was an additional mechanical factor heretofore not emphasized.

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Selected Abstracts

Ratliff, R. K., Nesbit, R. M., Plumb, R. T., and Bohne, W.: Nephrectomy for Hypertension With Unilateral Renal Disease. J. A. M. A. 133:296 (Feb. 1), 1947.

Of 2,055 pyelographic studies carried out in a five-year period, only 9 per cent of all the patients studied had abnormalities, while less than five per cent were candidates for nephrectomy and fewer came to operation.

Nephrectomy was performed on eleven patients who had hydronephrosis with significant hypertension. Five patients showed no permanent lowering of the blood pressure following operation, while two patients had moderate improvement and four had normal blood pressures which have persisted since the operation.

Of the latter group, two are significant in that they were known to have had normal levels of blood pressure prior to the development of advanced hydronephrosis and were followed for a time during which the development of hypertension paralleled the development of advancing hydronephrosis. In each of these instances, nephrectomy was followed by a return of the blood pressure to normal.

These authors suggest that routine urologic studies be performed on all hypertensive patients since a significant number of the patients having gross renal lesions could not otherwise be discovered.

BELLET.

Collins, C. G., Nelson, E. W., Jones, J. R., Weinstein, B. B., and Thomas, E. P.: Ligation of the Vena Cava—A Critical Evaluation Based on a Study of 22 Cases. New Orleans M. & S. J. 99:488 (April), 1947.

The authors feel that patients with post-partum or postabortal sepsis who fail to respond to nonsurgical measures should be considered as candidates for ligation of the normal venous return from the uterus, the vena cava, and both ovarian veins. In addition to suppurative pelvic thrombophlebitis, these authors believe that ligation of the vena cava is indicated in cases of phlebothrombosis if the clotting process has extended into the external iliac or common iliac veins.

Of the twenty-two cases discussed, ligation was performed only in cases which failed to respond to all nonoperative measures advocated for suppurative pelvic thrombophlebitis, and these patients were the most acutely ill of all cases of puerperal sepsis seen by these authors. In the two patients in whom ligation was done for phlebothrombosis of the common femoral vein associated with uterine fibroids and the one case of postoperative suppurative pelvic thrombophlebitis, there were no deaths. In the nineteen patients with puerperal suppurative pelvic thrombophlebitis who were operated on, there were four operative deaths. All patients showed remarkably good compensation of the circulation following ligation. The end results and the appearance of the patients' extremities were very good.

The authors state that ligation of the inferior vena cava carries a low operative mortality and this procedure is one that should be used without hesitation when indicated. The minimal amount of edema and circulatory disturbance occasioned by vena cava ligation, they believe, was due to the fact that at the time of operation the sympathetic chains were sectioned. If this is not possible at operation, they suggest routine blocking of the lumbar sympathetics bilaterally daily for five or six days after operation.

BELLET.

Johnson, A. L., Wollin, D. G., and Ross, J. B.: Heart Catheterization in the Investigation of Congenital Heart Disease. Canad. M.A.J. **56**:249 (March), 1947.

This report is based upon a group of seventeen children with congenital heart disease, in which this method of study has been employed. The patients ranged in age from 19 months to 16 years. Four were cyanotic and the remainder acyanotic. During the investigation all four heart chambers were entered, as well as the pulmonary artery and its branches, and the pulmonary veins.

In the study of a congenital heart by this means, samples of blood were withdrawn from various parts of the heart and pulmonary tree. From a correlation of the oxygen content of the blood with the pressure exerted and the site of the catheter at the point where these observations were made, the course of the blood flow might be traced.

The procedure employed is similar to that described by Cournand and Ranges. The median cubital vein of either arm or the saphenous vein in the thigh is exposed, and a uretal type of catheter is introduced through a nick in the vein. The catheter is introduced under fluoroscopic vision, passing into the right auricle, right ventricle, and the pulmonary artery and its branches.

Penicillin is given intramuscularly for forty-eight hours following the procedure, 5,000 to 10,000 units every three hours, depending on the age of the child. The pressure is recorded by a saline manometer and a Tycos dial.

Right heart catheterization is generally regarded as a safe procedure.

These authors report no arrhythmias, apart from extrasystoles due to the stimulation of heart catheterization. In one case a paroxysmal tachycardia occurred after the catheter had been placed in the right auricle and apparently through the auricular septum into the left auricle.

Furthermore, apart from occasional instances of slight thrombophlebitis of the brachial vein, no residua of trauma to endothelial linings have been described. In this respect the authors report a case of an ill, markedly cyanotic infant weighting 19 pounds, with a hemoglobin of 22 Gm. per cent. The catheter was introduced into the right saphenous vein near the femoral junction and passed into the right auricle. The infant was heparinized for the duration of the procedure. One month following this procedure death occurred. Autopsy revealed a clinically unsuspected, well-organized thrombus occluding the inferior vena cava, both common iliac veins, and the right renal vein, and a large thrombus attached to the right auricular wall at the base of one leaflet of the tricuspid valve.

Of the seventeen patients studied, nine were considered to have interventricular septal defects, in one there was evidence of an associated interauricular septal defect, and in another, the presence of a persistent left superior vena cava was demonstrated.

The evidence for the presence of a ventricular septal defect is arterialized blood in the right ventricle, or blood with a significantly higher oxygen content than that found in the right auricle.

In the course of this study, the authors observed during the placing of the catheter under fluoroscopic vision, that an excellent estimate of the size of the right ventricle could be made.

This method of heart catheterization, in the experience of the authors, appears a most useful adjunct in the investigation of congenital heart disease. BELLET.

Dungal, Niels: Cardioaortitis. Arch. Path. **42**:495 (Nov.), 1946.

The author reports a case of marked productive inflammation, particularly of the abdominal aorta. A man, 22 years of age, had had recurring attacks of polyarthritis with fever for ten years. In addition, glandular enlargements, particularly in the neck, made their appearance and became more or less chronic. Following recurring arthritis there was moderate secondary anemia and leucopenia, the cause of which remained uncertain. All bacteriologic and serologic diagnostic testing was negative. The patient eventually died of uremia.

Autopsy revealed cardiac hypertrophy, large nephrotic kidneys infiltrated with amyloid, an enlarged spleen weighing 700 grams, and caseous lymph nodes in the neck and in the mediastinum. Of particular interest was a productive inflammatory thickening of the walls of the abdominal aorta. Repeated section of the aortic wall did not reveal evidence of the ordinary atherosclerotic and calcific changes usually encountered in degenerative aortic disease. Microscopically the lesion was featured by increased thickness of the wall due mainly to thickening of the intima.

The thickening was mainly the result of hyaline infiltration containing foci of cellular infiltrations; consisting of neutrophil leukocytes, endothelioid cells, and histiocytes in a background of necrotic tissue, accompanied by hemorrhages of varying degree. The vasa vasorum were frequently surrounded by plasma cells and small heaps of lymphocytes. The muscular tissue was largely replaced by fibrosis and numerous small and large fluid-filled spaces were seen, suggesting colliquative necrosis. Microscopic examination of the myocardium revealed numerous small interstitial accumulations of lymphocytes and monocytes and a few plasma cells.

The writer points out that syphilis, which is considered the most common cause of productive aortic inflammation, was clearly absent in this case and that clinically no evidence of syphilitic infection had been found. It was felt with equal certainty that another great cause of microscopic aortitis, rheumatic fever, was absent in this case since there was no cardiac valvular pathology. Due consideration was given to the clinical history of recurring polyarthritis. The author did not feel justified in assuming that streptococcic infection might be the basis of the changes, since cultures from the spleen and the heart remained sterile.

Dungal selected similar cases from the literature in which various authors were convinced that syphilis played no role in the development of the aortic lesions. He believes this may be a case of focal aortitis related to the lesions of vascular allergy as described by Rich. The presence of chronic tuberculous infection, in the author's opinion, did not appear to have any causal relationship. He emphasized the growing caution in the minds of many pathologists against making a blanket diagnosis of syphilitic aortitis where the aorta shows an obvious, but not clearly defined, type of inflammation. GOULEY.

Deschamps, P. N.: A Case of Prolonged Flutter. Arch. d. mal. du coeur. **39**:233 (July-Aug.), 1946.

An unusual case of auricular flutter is reported in which the abnormal rhythm persisted for a period of over two years. The patient, a 36-year-old woman, had rheumatic heart disease with mitral stenosis and insufficiency. The auriculoventricular response was 2:1 during exercise and 4:1 at rest. It was noteworthy that, with the exception of occasional brief intervals of mild congestive failure, the patient was able to continue her daily activities with little or no discomfort. More remarkable was the fact that repeated attempts to terminate the arrhythmia by digitalis and quinidine therapy were totally ineffectual and that ultimately, at a time when no medication was being taken, the arrhythmia ceased spontaneously. LAPLACE.

Macht, D. I.: Thromboplastic Properties of Digitaloids and Mercurial Diuretics Employed in Cardiology. Arch. internat. de pharmacodyn. et de thérap. **72**:297 (Sept.), 1946.

Experimental studies on cats and rabbits were undertaken to supplement the previous observations of the author on the thromboplastic properties of digitalis. It was found that digitalis and ouabain injection caused a progressive shortening of the coagulation time of whole blood which paralleled the repeated injections. The minimum lethal dose of digitalis and ouabain for a heparinized cat was larger than for a normal cat; this increased tolerance was attributed to inhibition of the thromboplastic effect. The mercurial diuretics, mercupurin, mercuhydrin, and salyrgan, likewise accelerated blood clotting. They decreased the prothrombin time, decreased antiprothrombin, and increased blood fibrinogen, but did not affect the platelet count or the blood calcium. Occasional instances of sudden death in the course of digitalis or mercurial diuretic therapy are attributed to this thromboplastic action. LAPLACE.

MacMillan, R. L.: Adrenal Apoplexy Associated with Hypertension. Lancet **1**:177 (Feb.), 1947.

The author presents the history of a 60-year-old patient with pre-existing hypertension who suddenly developed severe upper abdominal pain which later became localized in the epigastrium. A clinical diagnosis of coronary occlusion was made. On the following day, after developing shock, the patient died. Autopsy revealed hemorrhage in both adrenal glands as the cause of death. This case is considered to be of interest since it emphasizes the fact that adrenal hemorrhage may occur in other conditions than septicemia (Friderichsen-Waterhouse syndrome).

The author states that adrenal apoplexy has never been diagnosed either clinically or at operation. He suggests that adrenal hemorrhage may be (1) associated with involution or destruction of gland substance in (a) the newborn, (b) pregnancy, (c) invasion by tumor; (2) caused by damage to blood-vessel walls by (a) toxemia (burns), (b) trauma, (c) septicemia (Friderichsen-Waterhouse syndrome), (d) arteriosclerotic change; (3) associated with hypertension; (4) associated with a generalized hemorrhagic tendency, as in leukemia and in vitamin K deficiency in the newborn.

BELLET.

Gurvich, N. L., and Yuniev, G. S.: Restoration of Heart Rhythm During Fibrillation by a Condenser Discharge. Am. Rev. Soviet Med. 4:253 (Feb.), 1947.

In 1938 these authors developed a condenser method for terminating cardiac fibrillation caused by electric shock. They used a condenser battery with a capacity of 3-4 microfarads. The condensers were charged by a small step-up transformer, with the aid of a rectifier. In order to restore the heart function the condenser had to be charged with more than 2,000 volts, depending upon the size of the animal. Later, these authors studied in detail the physical and physiologic conditions which terminated cardiac fibrillation by a condenser discharge.

Six hundred fifty dogs, sheep, and goats were used. In the majority of cases no narcotics were given. Cardiac fibrillation was produced by passing through the electrode an alternating current of 0.1 amperes or greater intensity. Fibrillation was stopped by condenser discharges. Capacity fluctuated between 0.5 and 52 microfarads; the tension which was applied reached as high as 6,000 volts.

The importance of the prolongation of discharge for the termination of fibrillation was indicated. The condenser discharge restored cardiac function if the discharge was applied not later than one to one and one-half minutes after the onset of fibrillation. However, by means of preliminary massage of the heart, normal cardiac function may be restored by discharges applied after a considerably longer period of fibrillation.

The above tests made on fifty dogs showed that after fibrillation lasting 8 minutes, the animals were easily resuscitated. When it had lasted ten to fifteen minutes nineteen animals survived and seventeen died. Thirteen of the latter had been weakened by previous operations.

The condenser discharge is effective in checking cardiac fibrillation in animals caused by electric shock as well as by certain poisons (chloroform, potassium chloride). The cardiac rhythm returned and resembled the original rhythm which was recorded before the occurrence of fibrillation. The re-establishment of normal heart action and of the function of the central and sympathetic nervous systems is lasting, as indicated by animals observed from ten days to four months.

The experiments suggest that the condenser method of reestablishing the normal heart action in ventricular fibrillation may be just as effective in cases of electric shock in man.

BELLET.

Teplich, J. G., and Drake, E. H.: The Roentgen and Cardiac Manifestations of Funnel Chest. Am. J. Roentgenol. 56:271 (Dec.), 1946.

The authors present a review of nine cases of funnel chest. The roentgen changes, electrocardiographic and clinical findings, and the salient features of the literature are presented.

This deformity greatly lessens the anteroposterior diameter of the chest and displaces the heart to the left. Rotation of the heart along its long axis may also result.

The x-ray findings are quite characteristic. In the posteroanterior view the heart is shifted to the left with elevation of the left border. Unless the true situation is realized, this configuration may erroneously be interpreted as congenital heart disease, mitral disease, or an enlarged heart.

Minor electrocardiagraphic abnormalities are frequently present, particularly in the chest leads. These are due to a shift of the heart to the left and rotation on the long axis, rather than to myocardial pathology. The authors describe an unusual case with bigeminal rhythm due to

regularly recurring right ventricular extrasystoles, which was probably due to an irritable focus in the right ventricle resulting from constant pressure of the deformed sternum in this region.

The authors feel that uncomplicated nontraumatic developmental funnel chests usually do not produce symptoms of a serious nature and surgical elevation of the sternum is rarely indicated.

ZION.

Puddu, V., Mussafia, A., and Giordano, G.: An Unusual Electrocardiographic Pattern of Myocardial Infarction. (Type $QT_1C_{5\text{-}6}$). Cardiologia **11**: 133, 1947.

Three patients are reported with definite electrocardiographic changes of an anterior wall infarct in the limb leads and with normal chest leads (CF_3 and IVF, or CR_3 and IVR). It is pointed out that these changes combine some of the features of an anterior wall and supra-apical infarction pattern (normal IVR). The changes in the limb leads point to a localization not far from the apex and might be near the apex in the lowest portion of the lateral wall. The terms "lateral para-apical" or "inferior lateral" infarction are suggested. This view is further supported by a series of normal and pathologic patients in whom Lead CF_5 was taken. They usually showed identity of form of QRS in Leads I and CF_5. Two further patients are reported with anterior wall infarction pattern in the limb leads, normal CR_3 and IVR, and Leads CR_5 or CR_6 resembling Lead I.

Only five such cases were found in more than 200 cases of infarction and, therefore, are considered rare.

LENEL.

Sanabria, A.: 2-Thiouracil in Heart Failure and in Angina Pectoris. Cardiologia **11**:143, 1947.

Seven patients with heart failure or angina pectoris treated with thiouracil are reported. Whenever a fall of the basal metabolic rate (in one case as low as —28 per cent) was obtained, definite improvement of heart failure and angina pectoris followed. The basal metabolic rate fell several weeks after administration of thiouracil was started. This was associated with an increase in blood cholesterol.

Two patients showed evidence of drug toxicity and no reduction in the basal metabolic rate. In both the drug was discontinued. One patient died on the eighteenth day of therapy. Four patients had a satisfactory response.

In conjunction with thiouracil therapy, liver extract, folic acid, piridoxine, bone marrow extract, vitamin C, sodium bicarbonate, and a low fat diet are given.

LENEL.

Lindgren, I.: High Oxygen Concentration Under Normal and Increased Respiratory Pressure in Cardiac Pain and in Pulmonary Edema. Cardiologia **11**:127, 1947.

The pain in angina was relieved and the electrocardiogram with typical signs of coronary insufficiency at rest showed improvement during oxygen administration. The beneficial effect of 100 per cent oxygen administered under increased respiratory pressure was demonstrated in a case of coronary occlusion with pulmonary edema.

It is pointed out that 100 per cent oxygen increases the oxygen saturation in the blood and plays an important role under pathologic conditions. Increase in oxygen tension during positive pressure administration tends to increase the oxygen saturation of the arterial blood. A closed or semiclosed system must be used when positive pressure is given. It is pointed out that the vicious circle in pulmonary edema is interrupted by the use of oxygen under positive pressure. In the previously mentioned patient 10 mm. Hg positive pressure was used; this can be administered only in unconscious patients.

This therapy has also been found beneficial in eclampsia with or without cardiac failure. The case of a primipara is reported who had been unconscious for twenty-two hours after delivery with attacks of eclampsia and progressive pulmonary edema. Strophanthin, hypertonic glucose, venesection, and oxygen by nasal catheter had no effect. 100 per cent oxygen under 10 mm. Hg pressure produced rapid and striking improvement.

LENEL.

Batt, R. C.: A Roentgenkymographic Study of the Heart in Myasthenia Gravis. Radiology **46**:374, 1947.

Early kymographic studies of myasthenic patients showed a slight slowing of the pulse with minor but definite changes in the wave form along the left ventricular border after a test dose of prostigmine. Similar kymographic changes could be obtained in normal subjects used as a control; thus indicating that the changes were due to the pharmacologic effects of prostigmine. There were, however, wave form changes which at first could not be accounted for. It is well known that any change in the ratio between the grid speed and the heart rate will affect the appearance of the kymographic wave form. Patients with myasthenia gravis, as well as normal patients, were studied before and after prostigmine test doses with various grid speeds. The results in all cases were identical. This indicated that the major changes in shape of the kymographic wave produced by prostigmine represents artefacts due to the changing ratio between heart rate and grid speed.

These studies showed that there are no characteristic findings in the cardiac roentgenkymograms of patients with myasthenia gravis. The prostigmine test produces no characteristic cardiac kymographic wave changes in either normal or myasthenia gravis patients. The test doses may slow the cardiac rate and thereby produce deceptive changes in wave form.

ZION.

Terroux, K. Godwin, Gertler, M. M., and Hoff, H. E.: The Alkali Tolerance of the Dog Heart. Am. J. Physiol. **148**:1 (Jan.), 1947.

In determining the alkali tolerance of the dog heart in situ, twenty-four dogs were used by the authors, and these were infused with 0.3 normal sodium hydroxide in most cases. Blood samples were drawn from a femoral artery, as were the samples for lactate determinations. Electrocardiograms were taken from Lead II at intervals corresponding to 50 c.c. increments of infusion fluid.

The results of the experiments fall into three groups. In Group I the dogs died in the initial stages of the experiment, either because of a high initial rate of alkali infusion or because of some individual sensitivity to alkali. Severe anoxia occurred in all these cases. In Group II the infusion rates were low and blood lactate did not rise above 100 mg. per cent. These hearts failed at pH values between 7.7 and 7.93. In Group III the overall injection rates were higher than in Group II. These animals showed rigor of the respiratory muscles, as well as of some other muscle groups, accompanied by an increase in the blood lactate level with values up to 200 mg. per cent. The blood pH rose as high as 8.12 to 8.40 before heart failure. Blood pressure was well maintained until the final failure of the heart. In the electrocardiogram, the most interesting changes were in the T wave which became lower in amplitude as the pH rose, with complete reversal of polarity either before or at the time of the first maximum pH. RS-T segment depressions were observed just before heart failure occurred, indicating that this was significant of impending trouble. The R wave changed only in the final stages. Heart rate was essentially unchanged. Intraventricular conduction time was unchanged. Auriculoventricular conduction time was increased in four experiments, decreased in six, and unchanged in five. The value of K in Bazett's formula was unchanged in three experiments, decreased in five, and increased in eight. There was no change in respiratory movements until the pH rose above 7.8. The mode of death was ventricular fibrillation or failure of myocardial contractility. The phenomenon of cardiac action currents stimulating somatic nerves was found in three cases.

BERNSTEIN.

Wilens, S. L.: Bearing of General Nutritional State on Atherosclerosis. Arch. Int. Med. **79**:129 (Feb.), 1947.

The author points out that in spite of various reports, such as those of French and Dock that overweight and atherosclerosis are definitely connected, other equally definite statements, such as that of Weiss and Minot in 1933, and of Wright in 1943, lead one to believe that "there is no proof that overnutrition leads to atherosclerosis in man."

However, taking his data from 1,000 consecutive autopsies performed in the Bellevue Hospital in New York, and 250 consecutive autopsies on obese persons over the age of 35, Wilens attempts to demonstrate statistically the close relationship between obesity and atherosclerosis.

The series is divided into three groups, according to the state of nutrition as evaluated at autopsy. The statement as to the general state of nutrition recorded in the protocol was generally accepted in making this classification. The author points out that some inaccuracy was unquestionably involved in this method. However, as a general rule, the state of body at necropsy is less likely to show evidence of obesity than at any other time.

The patients of each nutritional group were reclassified by the degree of atherosclerosis present into the following categories: (1) Those with no atherosclerotic lesions anywhere in the arterial system, or only slight ones; (2) those with lesions of moderate degree; and (3) those with severe and widespread lesions. Here again, the pathologist's estimate, as recorded in the protocol, was accepted. The author again admits that such a method is open to criticism.

The statistical analysis of data yielded the following results:

In each sex, atherosclerosis was definitely more marked in the obese group than in the average group, and more marked in the average group than in the poorly nourished group. This was true in the peripheral as well as the coronary arteries. Obese women appeared to have a somewhat lower incidence of severe atherosclerosis than obese men. A similar result again prevailed when the results were analyzed with respect to age, hypertension, heart weight, and the presence or absence of diabetes.

The author concludes that although the analysis is based on the state of nutrition as observed at necropsy, evidence is presented to show that if the analysis had been based on the probable state of nutrition prior to the onset of the final illness, the relationship between atherosclerosis and nutrition would be even more striking.

HORWITZ.

Plotz, M.: Bronchial Spasm in Cardiac Asthma. Ann. Int. Med. **26**:521 (April), 1947.

On the basis of improvement in the vital capacity which followed within thirty seconds the subcutaneous injection of 0.5 c.c. of a 1:1000 solution of epinephrine in nine cases of heart failure, the author concludes that bronchial constriction, reflexly induced, is the basic difficulty in cases of cardiac failure with so-called "cardiac asthma." By contrast, in eleven cases of severe heart failure with basal pulmonary congestion without wheezing, the administration of this drug did not result in any significant increase in the vital capacity. The author regards as untenable the possibility that the drug ameliorated the symptoms by increasing the heart action, or by decreasing submucosal edema, or by relieving congestion in the interalveolar framework.

WENDKOS.

Seldin, D. W., Kaplan, H. S., and Bunting, H.: Rheumatic Pneumonia. Ann. Int. Med. **26**:496 (April), 1947.

The clinical, roentgenographic, and pathologic findings in six fatal cases of active rheumatic fever with carditis, complicated by rheumatic pneumonia, are summarized. A uniform clinical picture, characterized by an abrupt onset of profound respiratory distress in the absence of commensurate physical signs in the chest, was encountered in all instances. Hacking cough with scanty, blood-streaked sputum, moderate to high fever, and leucocytosis were also present. In the roentgenogram, the process was manifested by bilateral, multilobar, nonsegmental infiltrations resembling the shadows produced by pulmonary edema.

The histologic lesions could be included in one or more of five categories: (a) an edematous infiltration of the alveolar walls and interstitial tissues ultimately becoming replaced by endothelial cells and fibroblasts; (b) an accumulation of exudate in the alveoli consisting of fibrin, edema, polymorphonuclear leucocytes, mononuclear and multinuclear phagocytic cells ultimately undergoing organization; (c) a hyalinized fibrinous pseudomembrane lining the small bronchioles, believed to be the result of intra-alveolar material being forced upward by inspiratory effort during an attack of dyspnea; (d) vascular lesions in the pulmonary capillaries and arterioles which

ranged from intracapillary hyaline thrombi to intramural and perivascular cellular infiltrations involving the arterioles; and which were subsequently transformed into hyalinization of the intima, scarring of the media, and perivascular fibrosis; and (e) the occasional observation of a parenchymal lesion which resembled the Aschoff body.

WENDKOS.

Welin, S., Hamberger, C. A., and Crafoord, C.: Surgically Removed Foreign Body Embolus in the Pulmonary Artery. J. Thoracic Surg. **15**:302 (Oct.), 1946.

The authors report a case of a 21-year-old workshop apprentice who was sent to the otolaryngolgic clinic with the diagnosis of foreign body in the left lung. He gave the following history: a splinter from an iron wedge had struck him and entered the left groin. An aneurysm developed, for which an operation was performed. Since then he had occasional pain and swelling in the left leg and phlebography showed a defective reflux from that leg. About a year later the patient was referred to the medical clinic with the diagnosis of incipient pneumonia. Roentgen examination at this time disclosed a small bronchopneumonic-like induration with atelectasis at the base of the left inferior lobe and behind the heart. In the bronchus situated in the posterior basal part of the left inferior lobe, about 7 cm. distal to the carina, a very dense, irregularly-shaped foreign body, nearly 1 cm. in length, over 1 mm. in thickness, and from 7 to 8 mm. in breadth, was also revealed. During bronchoscopy a sound and extractor were inserted in the left bronchial branch, but failed to remove the foreign body. The patient was finally operated upon and it was found that the foreign body was fastened in the part of the artery wall adjacent to the bronchus. The foreign body was removed without any complications. There were no clinical or roentgenologic signs of a disturbance of the circulation in the inferior lobe of the left lung, which indicated that no thrombosis developed in the open pulmonary artery.

The authors point out that the foreign body had entered the femoral vein and had been thrown by the blood stream into the pulmonary artery. The ordinary x-ray examination failed to show the position of the foreign body in relation to the bronchial tree, and bronchoscopy alone did not clear up the matter. Location of the foreign body was only made possible through the combination of these two methods.

They report this to be the first case where the diagnosis of foreign body embolus in the pulmonary artery has been made prior to operation and where the foreign body had afterward been extracted by thoracotomy plus arteriotomy followed by vascular suture.

BELLET.

Shumacker, H. B., Jr., and Abramson, D. I.: Sympathectomy in Trench Foot. Ann. Surg. **125**:203 (Feb.), 1947.

The authors describe trench foot as a syndrome which follows prolonged exposure of the foot to a wet and cold environment. Physiologic and pathologic alterations may lead to necrosis of tissue in extreme instances and damage to muscles and nerves may occur, followed by fibrosis, atrophy, contractures, sensory disturbances, and pain on weightbearing. Intense vasospasm, noted initially, may be replaced by a transient period of hyperemia and later followed by a return of excessive tonus which persists.

Of 700 patients admitted to the hospital with trench foot, forty-nine were subjected to sympathectomy (removal of the second and third lumbar ganglia with the intervening chain) involving sixty-six lower extremities. Three main groups were analyzed: (1) those with extensive gangrene; (2) those with excessive sympathetic tonus; and (3) those with the complaint of pain on weightbearing.

The results showed that sympathectomy had a favorable effect on the acceleration of the rate of healing of lesions in patients with extensive gangrene associated with vasospasm. It was also useful in treating maceration of skin and secondary infections resulting from prolonged hyperhidrosis. Sympathectomy reduced the severity of symptoms in patients suffering from cold sensitivity, but produced variable results in the treatment of pain due to weightbearing.

LORD.

Addari, F., de Carolis, D., Montevecchi, M., Foscarini, M., Curti, A., Sita, A., Altanta, G., Josonni, D., Rizzo, S., Tavoschi, F., Magoro, G., and Grandi, F.: Clinical and Experimental Studies of Sympathomimetic Compounds (Sympatol, Veritol, Sympamina), Part 1 to 13. Folia Cardiologica 5:198 (August), 1946.

In forty normal subjects given the three sympathomimetic substances orally, intramuscularly, or by vein, bradycardia was noted preceding the maximum rise in blood pressure. This was striking with Sympatol and Veritol and is blamed partly on a secondary vagal effect caused by the rise in arterial pressure and partly on a direct action of the substances on heart muscle. Following Sympatol and Veritol, the arterial blood pressure rose in all instances as the result of both an increased cardiac output and peripheral vascular constriction. Rise in pressure after the administration of Sympamina occurred apparently exclusively on the basis of peripheral vasoconstriction. Oscillometric indices increased, especially following Veritol. Venous pressures were found to rise, which was particularly striking upon the administration of Sympamina. A preliminary fall in venous pressure was often noted.

No striking electrocardiographic changes were present after Sympamina. Sympatol caused prolongation of Q-T interval, extrasystoles, nodal rhythms, and occasional prolongation of A-V conduction. In one instance, transient auricular fibrillation was noted. Similar changes may be induced by Veritol and resembled the effects of intravenously injected epinephrine or a combination of sympathetic and parasympathetic compounds. Phonocardiograms revealed a regular increase in the intensity of all heart sounds suggesting a positive inotropic effect exerted by these agents.

Sympatol and Sympamina caused a definite increase in circulating blood volume (method not given) as the result of peripheral vasoconstriction (spleen), while the administration of Veritol was followed by a diminution of blood volume due to pulmonary congestion.

Cardiac output, determined by gas analytic methods and by the pulse volume curves of Boeger and Wetzler, revealed a constant increase with all three substances but was most pronounced following the administration of Sympatol. Sympatol and Veritol increased cardiac output by a direct positive inotropic action on the heart muscle, Sympamina accomplished this by increased cardiac filling secondary to peripheral venous constriction. Oxygen consumption appeared to be increased with all three compounds. Changes in the dynamics of the arterial system were investigated by the use of the sphygmographic analysis of Wetzler and Boeger. Based on measurements of pulse velocity, Veritol constricts the central arterial system (aorta and large vessels), more so than Sympamina and Sympatol. Peripheral resistance appeared to be decreased following Sympatol. This is caused perhaps by splanchic dilatation overbalancing the effects of vasoconstriction induced in cutaneous areas. Peripheral resistance is greatly increased following the administration of Veritol and Sympamina, which suggests a more diffuse arteriolar constriction. Increase in arterial tension caused by Sympatol, therefore, is assumed to be the result of increased cardiac output, that following Veritol and Sympamina must be considered as a combination of central and peripheral effects.

Red blood cell counts and hemoglobin values rose after the administration of all three agents. Increase in total leucocytes with relative lymphocytosis was commonly observed but occurred particularly after the administration of Sympamina. Increase in red cell count and hemoglobin values are explained by the emptying of blood depots; rise in leucocytes, by contraction of the spleen.

Blood glucose levels rose in response to Sympatol and Sympamina but not following the administration of Veritol. The rise is explained partly by excessive glycogenolysis from the liver and partly by decreased absorption of glucose from the constricted capillaries.

Sympatol administration was followed by but little change in urinary volume, but caused a constant increase in glomerular filtration (creatinine clearance) and in tubular reabsorption (glomerular filtration minus urine volume). Veritol caused diuresis by an increase in glomerular filtration. A similar diuretic effect of Sympamina appeared as the result of decreased tubular reabsorption without striking alteration in glomerular filtration.

Constriction of capillaries was noted together with a long lasting increase in capillary pressure following the administration of all compounds (method of Salvioli).

No striking alterations were noted in spinal fluid pressures. The rise following bilateral pressure on the jugular veins was diminished following the administration of these compounds (general vasoconstriction).

Topical application of all compounds caused mydriasis. This was particularly striking following the instillation of Veritol (0.5 per cent solution).

HECHT.

Carlgren, L. E.: Gallop Rhythm in Children Studied by Means of Calibrated Phonocardiography. Acta paediat. **33:** Suppl. 6, 1946.

A review of the etiology and characteristics of third heart sounds, auricular sounds, and various types of gallop rhythms is presented. The view is expressed that the third sound is caused by vibrations of the ventricular wall secondary to the rapid inrush of blood into the ventricles during early diastole. The auricular sounds are presumed to be formed by vibrations of both the ventricular muscle and the atrioventricular valves. An attempt is made to separate the normal third heart sound from protodiastolic gallop rhythm, and the normal auricular sound from an auricular gallop by the use of Mannheimer's "calibrated" phonocardiograph. This instrument transmits the response of the recording microphone through various selective high and low pass filters to four oscillograph coils. A series of different frequency bands of heart sounds or murmurs may thus be recorded by separate channels simultaneously. The units are selective for frequency ranges of 0 to 175, 100 to 250, 175 to 400, and 250 to 1,000 cycles per second respectively.

In children, the normal third heart sounds and the auricular sounds are of low voltage and display frequencies below 100 oscillations per second. Gallop rhythms occurring during the same phase of the cardiac cycle reveal greater amplitudes and have frequencies considerably above 100 cycles. Using these criteria, gallop rhythm was recognized in 104 children. Seventy-eight revealed protodiastolic gallop rhythms; two, auricular gallop; and twenty-four were classified as presenting a summation type of gallop. In sixty-four of these children no apparent heart disease was present, but in one-half of these myocardial damage could not be ruled out with certainty. Gallop rhythms of this type were frequently found in acute rheumatic fever but occurred only five times in 300 instances of congenital heart disease.

Gallop rhythms occurred in rabbits four to six days following the injection of caffeine (0.25 Gm. per kilogram) and 0.2 mg. of epinephrine intravenously (Fleisher and Loeb). Myocardial lesions were thus produced in twenty-three of thirty rabbits and gallop rhythms were present in sixteen of the twenty-three animals. It was always found to be associated with excessive cardiac dilatation as demonstrated by x-ray. This favors the concept that a diminished tone of myocardial muscle is a prerequisite for the gallop rhythms.

HECHT.

Magro, G.: Intraventricular Conduction on Exercise: A Cardiac Function Test. Folia Cardiologica **5:**439 (August), 1946.

A method previously reported by Pachioli has been employed in which the duration of the QRS complex is measured before and after exercise (step test). The QRS complex before and after the test was enlarged and its duration measured with an accurate comparator. In ten normal individuals and in ten patients with cardiac neurosis a slight decrease in the width of QRS was noted, the degree being directly proportional to the increase in heart rate. Patients suffering from a variety of organic diseases of the heart revealed a prolongation of QRS in most instances. The test is claimed to be of value in cases where organic heart disease is suspected in the face of normal electrocardiographic or roentgenographic findings at rest.

HECHT.

Gregersen, Mangus I., and Root, Walter S.: Experimental Traumatic Shock Produced by Muscle Contusion With a Note on the Effects of Bullet Wounds. A Study of the Clinical Signs of Shock in the Dog and of the Role of Blood Volume Reduction in the Development of the Shock Syndrome. Am. J. Physiol. **148:**98 (Jan.), 1947.

Experimental traumatic shock was produced in thirty dogs by uniform contusion of the thigh muscles on the anesthetized animal. Only one dog failed to show the characteristic signs of shock.

These signs consisted of the following: (1) fall in blood pressure; (2) tachycardia; (3) fall in rectal temperature; (4) signs of peripheral vasoconstriction, (a) cold extremities (progressive), (b) dry, lifeless appearance of the oral mucous membranes, (c) disappearance from view of the superficial veins; (5) evidence of thirst and vomiting after taking fluids while in shock; (6) central nervous system depression; (7) decrease in plasma volume (35 per cent or greater); and (8) hemoconcentration. Although this report was concerned only with observations made on thirty animals, subsequent investigations carried out in the same laboratory on many other traumatized dogs have confirmed in every respect the results noted.

Muscle trauma which was severe enough to reduce the blood volume by 30 per cent or more invariably produced shock, and the shock was usually fatal. The blood volume was reduced at, or shortly after, injury and remained unchanged for several hours. The loss of fluid occurred only into the injured area and was fully accounted for by the decrease in blood volume and mobilization of fluid from uninjured areas.

These results, supported by subsequent investigations, refute the concept, at one time widely accepted, that the fundamental cause of shock is a general increase in capillary leakage.

BERNSTEIN.

Wang, S. C., Painter, E. E., and Overman, R. R.: The Mechanism of Prolonged Fluorescein Circulation Time in Experimental Traumatic Shock. Am. J. Physiol. **148**:69 (Jan.), 1947.

Reliable evidence previously reported by the authors indicates that changes in fluorescein circulation time can be used as a simple prognostic index of the condition of dogs after muscle trauma. The fluorescein circulation time showed a gradual increase during the period of incipient shock in those animals which eventually died. In contrast to this progressive increase, simultaneously determined cyanide circulation time increased to a value which was maintained at a plateau until the mean blood pressure fell below 50 mm. Hg when it underwent a further increase. To determine the mechanism of the discrepancy just noted, bilateral upper thoracic sympathectomies were performed on eleven dogs under intravenous nembutal anesthesia, followed in five to seven weeks by trauma to produce shock. On the day before these trauma experiments, control circulation time and plasma volume were determined.

Since the control fluorescein circulation time was only one or, at most, two seconds longer than the control cyanide time, the increasing difference between the two methods in shock must be accounted for by some factor other than the greater distance involved in the measurement by fluorescein. The discrepancy between the two methods indicates a progressive impairment of the peripheral systemic circulatory apparatus in traumatic shock, which is revealed only by the fluorescein method.

In the dogs subjected to sympathectomies, the fluorescein circulation time following trauma behaved in the same manner as did the cyanide circulation time in the normal traumatized animals. These facts indicate that the mechanism of the prolongation of fluorescein circulation time in the normal dog in traumatic shock is associated with an increased activity of the sympathetic nervous system, particularly upon the peripheral portion of the vascular tree.

BERNSTEIN.

Young, R. D., and Hunter, W. C.: Primary Myxoma of the Left Ventricle With Embolic Occlusion of the Abdominal Aorta and Renal Arteries. Arch. Path. **43**:86 (Jan.), 1947.

The authors report a case of primary tumor of the heart originating in the left ventricle. The patient, a 10-year-old white girl, had a previous history of recurring attacks of tonsillitis and of joint pains. The latter first appeared at the age of 5 years, and one year later a cardiac lesion was discovered.

The final illness was ushered in with leg pains, fever, and convulsions. Cardiac examination revealed a systolic thrill at the apex. Systolic murmurs were heard in both mitral and aortic areas, and there was also a diastolic aortic murmur. The spinal fluid pressure was increased but

the fluid was clear and there was no cell increase. Facial edema developed on the first day of hospitalization. There was anuria, and a catheter obtained only a few c.c. of bloody urine. The blood pressure was 150/84. Under sedation, the convulsions stopped but the anuria continued, as did hypertension and azotemia. The child died on the fifth day with uremia.

Necropsy, which did not include brain examination, showed an enlarged heart, thickened aortic leaflets, and a hypertrophied left ventricle. The latter contained multiple polypoid masses which almost filled the chamber, the largest being 5 x 3 x 2 centimeters. Most of these masses were soft and yellow, and all of them firmly attached to and springing from the wall of the ventricle by a common pedicle. The largest mass extended through the orifice of the aortic valve. A broken-off stump of a pedicle indicated the previous presence of another polyp which was found lodged in the abdominal aorta, blocking the orifices of both renal arteries and loosely attached by early organizing adhesion. The mass was yellow and spongy, similar to the growth in the left ventricle. The main renal arteries were plugged in their beginning by extension of this intra-aortic mass, and both kidneys were acutely infarcted. Thionine stain showed the cardiac tumor to be a myxoma, and similar structure was found in the aortic and renal embolism.

The case was unusual, insofar as embolic phenomena associated with cardiac tumors are rare. In this case another unusual feature was closure of both renal arteries by the embolism.

GOULEY.

Woll, E., and Vickery, A. L.: Primary Fibrosarcoma of the Heart With a Vertebral Metastasis. Arch. Path. 43:244 (March), 1947.

The authors report an instance of a very rare lesion: primary tumor of the heart with distant metastasis. The patient was a 47-year-old housewife who, in the course of three successive hospitalizations in a period of six months, showed a progressive disability of the right arm featured by numbness of the palm, atrophy of the interosseous and thenar muscles, and severe pain in the right shoulder and arm. The heart, at first of normal size, gradually became enlarged. In the first hospitalization a thrusting apical impulse was associated with a systolic mitral murmur. Later, a diastolic murmur was also heard, and leg edema developed. Clubbing of the fingers was progressively marked. Fever, bloody sputum, and progressive diminution of pulmonary aeration shown by x-ray studies were noted in the last hospitalization. At this time x-ray examination also revealed a loss of bone structure in the transverse process of the first thoracic vertebra, the process being "thin and hollow as if filled with expanding tumor." Death was caused by pulmonary insufficiency secondary to congestive heart failure.

Necropsy revealed almost complete occlusion of the mitral orifice by a yellow, firm, polypoid, somewhat lobulated growth, firmly and broadly attached at its base to the posterior wall of the auricle and to the posterior mitral leaflet. The growth was 4 cm. wide, 2.5 cm. high, and 3 cm. thick at the base. On cross section the growth fused with the endocardium and formed a course, paly gray, firm, homogeneous mass. The ventricular surfaces of the leaflets were smooth and glistening. The chorda tendineae were thickened, but not distorted. The other valves were normal. The endocardial surface of the left auricle was thickened and roughened. No other areas of tumor, thrombosis, or scarring were seen in the heart. The coronary vessels were normal. Histology revealed the auricular growth to be a spindle-cell fibrosarcoma. There was no evidence of muscle cell origin, nor was there any evidence of myxoma or angioma. There was microscopic invasion of the adjacent subendocardial tissue.

At the level of the first thoracic vertebra there was an ovoid, smooth mass, 5 cm. in length, 2.5 cm. wide, and 1.5 cm. high, firmly attached to the vertebral column, covering the latter and extending to the right over the attachment of the second rib. The tumor invaded and destroyed the underlying bony tissue and compressed the spinal nerve roots as they came out of the spinal canal. Microscopy showed it to be of the same fibrosarcomatous type as the tumor found in the heart.

The lungs showed evidence of prolonged congestion, sclerotic thickening of the pulmonary artery branches, fresh and old thromboses and pulmonary infarctions, and pulmonary fibrosis, as often seen in mitral stenosis.

The authors believe that the cardiac tumor was primary, since a metastatic tumor is usually multiple and involves the myocardium. In their opinion, it is unlikely that a metastatic lesion derived from the vertebral tumor would lodge in the left side of the heart without involvement of the lung. They state that there is no known case of solitary cardiac metastatic tumor. On the other hand, primary sarcoma of the heart generally originates in the auricular structure and frequently metastasizes to the lungs. This case, however, is the first showing metastatic involvement of the vertebral column.

GOULEY.

Handley, C. A., and Telford, J.: The Effect of Digitalis on the Fluid Distribution of the Body. J. Phamacol. & Exper. Therap. **89:**97 (Jan.), 1947.

Digitalis is known to reduce the blood volume and cardiac output of normal subjects. By measuring the blood volume (dye T 1824) and the extracellular fluid (thiocyanate "space") on dogs before and after digitalization, a further attempt was made to study this finding.

Digitalization produced a consistant decrease in plasma volume, rise in extracellular fluid, and rise in the hematocrit. The decrease in plasma volume may be explained by the pooling of blood in the liver and spleen. However, the rise in the hematocrit indicates that there was loss of fluid from the vascular system. The increase in extracellular fluid was far greater than could be accounted for by the escape of fluid from the plasma. Therefore, this extra water must come from the cells.

No explanation of these findings or therapeutic implications were drawn.

GODFREY.

Taylor. R. D., Corcoran, A. C., and Page, I. H.: Menopausal Hypertension: A Critical Study. Am. J. M. Sc. **213:**475 (April), 1947.

The female menopause, whether natural or artificial, has long been regarded as a cause of arterial hypertension, and the concept of "menopausal hypertension" has gained wide acceptance. Yet the evidence on which this view is based is largely derived from accumulated impressions rather than systematic study. With this in mind, the authors undertook the care of 200 menopausal women, 179 of whom had been surgically castrated and all of whom desired relief of menopausal symptoms. It was found that arterial hypertension was no more common in this group than in the general population. "Vasomotor instability," as exhibited by "hot flashes," perspiration, and tachycardia, are not necessarily associated with hypertension and their alleviation by estrogens need not affect arterial pressure. The menopause seemed to intensify pre-existing psychoneuroses. Despite severely neurotic behavior, hypertension did not develop within three or more years except in six of the subjects. From these data it is concluded that the relationship of the menopause and hypertension is incidental and loss of ovarian secretion is neither a primary nor a contributory cause of arterial hypertension.

DURANT.

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